NEUROSCIENCE INTELLIGENCE UNIT 6

S. Clare Stanford

Selective Serotonin Reuptake Inhibitors (SSRIs) Past, Present and Future

R.G. LANDES COMPANY

VISIT…

NEUROSCIENCE
INTELLIGENCE
UNIT 6

Selective Serotonin Reuptake Inhibitors (SSRIs)

Past, Present and Future

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NEUROSCIENCE INTELLIGENCE UNIT

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Past, Present and Future

R.G. LANDES COMPANY
Austin, Texas, U.S.A.

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PREFACE

As this book makes clear, the selective serotonin reuptake inhibitors (SSRIs) have turned out to have an impressive impact on the treatment of depression and one of them, fluoxetine, has even attained cult status. This success is a testament to the progress that has been made since the chance discovery of the antidepressant effects of imipramine in 1957. The attributes of the SSRIs have already been covered in several reviews of specific aspects of their pharmacology and clinical efficacy. Yet, so far, there has been no frank appraisal of the SSRIs which has tackled clinical and preclinical research of both their therapeutic actions and side-effects. The aim of this book was to plug this gap in the literature and draw on relevant material covering the whole spectrum of their actions: the 'cons' as well as the 'pros.' Obviously, their predecessors, the tricyclic antidepressants, are still the major comparator but, whenever enough is known, the latest pharmaceutical recruits have been drawn into the analysis too.

As with all projects of this type, this book was faced with the problem that the constituency of readers is as diverse as the chemistry of the SSRIs themselves, ranging from clinicians to basic scientists; from policy-makers and fund-holders to the health professional working at the coal-face; from those dedicated to drug discovery and development to those responsible for teaching in this complicated area; from the accomplished expert to the bemused student; from the pharmacologist to (possibly) the scientific correspondent. It is obviously impossible to satisfy all these different groups but we have done out best by ensuring that all chapters first cover background material before moving on to the more challenging specialist research. In so doing, this book has tried, wherever feasible, to bridge the chasms between the laboratory, the clinic and the lecture theater.

The book starts with a personal memoir of the discovery of the first SSRI, zimelidine, contributed by Arvid Carlsson who has been involved with these agents since the start of the story. The following seven chapters look at SSRIs from the clinical point of view. First, Pierre Baumann and colleagues describe the significance of their pharmacokinetics. In Chapter 2, they compare the different compounds and, in particular, highlight what is known about their metabolism and how this explains some of their adverse drug interactions. Here, and throughout the book, it is made clear that the SSRIs differ from the tricyclics in a number of respects, not least because they are a chemically unrelated group of compounds and so it cannot be assumed that they will all share the same phamacological profile.

In Chapter 3, Julie Newman and Andrew Nierenberg compare the SSRIs and tricyclics in all aspects of the treatment of depression and draw attention to the expanding list of disorders for which these drugs are proving to have a

beneficial effect. In fact, several authors allude to the expanding scope of licensed applications for these drugs and a whole chapter devoted to this topic would have been desirable. However, the chameleon therapeutic profile of the SSRIs probably merits a sequel in its own right.

The following chapters cover more controversial areas. John O'Brien and colleagues discuss the use of SSRIs in patients who present additional clinical difficulties (especially children and the elderly; Chapter 4). Heather Ashton and Allan Young (Chapter 5) deal with the vexed question of whether SSRIs carry a dependence-liability or whether, paradoxically, the converse is the case: that they can be used effectively in treatment of dependence on other drugs. Chapter 6 (Peter Sargent and Guy Goodwin) covers the effects of SSRIs on sexual function, an action which has turned out to be somewhat of a problem, and discusses clinical evidence in the context of what is known about the underlying physiology of sexual function. In Chapter 7, John Henry and Carol Rivas look at the question, which has caused considerable concern, of whether SSRIs cause, or prevent, suicide. Finally, recognizing that inhibition of 5-HT reuptake alone does not seem to account for the therapeutic effects of these drugs, Ian Anderson and Christopher Mortimore review the research using neuroendocrine challenges to help us gain some insight into how these drugs actually work in humans.

After this, the book concentrates mainly on preclinical material. In Chapter 9, Francesc Artigas and colleagues describe the long-term effects of SSRIs on serotonergic transmission in the brain and suggest explanations for the therapeutic lag and how this might be ameliorated. Complementing this, Clare Stanford (Chapter 10) appraises evidence for the 'selectivity' of the SSRIs and describes some routes by which these drugs could affect other monoamine systems in the brain. Fred Petty and colleagues (Chapter 11) go on to discuss the relevance of such changes to behavior in the rodent 'learned helplessness' model of depression. They not only suggest a scheme to explain how targeting the 5-HT brain system could have far-reaching effects on mood and behavior, which culminate in reversal of depression, but also describe how their ideas can be tested in humans.

The final chapter (David Heal and Sharon Cheetham) draws all this material together but looks at it from the perspective of those working in the pharmaceutical industry. Not only are pharmacological and clinical comparisons made between the tricyclics and SSRIs but, importantly, economic imperatives are exposed as well. We are also given valuable insight into the compounds that are in the pharmaceutical pipeline.

All the chapters are written by acknowledged experts to whom I am totally indebted for their investment of time and energy (and tolerance of my editorial whip!). However, whereas all the authors have clearly flagged the boundaries between fact and speculation, readers will be aware that they do not always express the same views. This alone points to areas of uncertainty where more research might be necessary. In fact, the first step in resolving such difficulties is to identify the controversies and this, too, has been an objective of the book.

Looking to the future, as more information accumulates, we will be able to take on a more rigorous comparison of the SSRIs with the next generation of antidepressants. In fact, it is interesting that, whereas the emphasis with the SSRIs (as is even indicated by their collective name) has been on their selectivity, recent developments have tended to move towards less selective agents, such as serotonin noradrenaline reuptake inhibitors ('SNRIs,' e.g., venlafaxine), or single molecule 'polypharmacy' such as the noradrenergic and specific serotonergic antidepressants (NaSSAs, e.g., mirtazepine). In so doing, drugs have emerged which have interesting combinations of monoamine reuptake inhibition and receptor interactions. Time will tell whether this leads to a significant leap forward for pharmacotherapy. Whatever the outcome, the statistics on suicide, outlined in Chapter 7, are a chilling reminder that we still have a long way to go in terms of developing antidepressant therapies which are even better and faster-acting than the SSRIs.

S.C. Stanford
October 1998

DEDICATION

For Stephen and the boys

ABBREVIATIONS

ACTH	Adrenocorticophic hormone
ATP	Adenosine triphosphate
BDI	Beck Depression Inventory
BMI	Body mass index
CGI	Clinical Global Impressions scale
CCK	Cholecystokinin
CNS	Central nervous system
COMT	Catechol-*O*-methyltransferase
*m*CPP	1-(*m*-Chlorophenyl)piperazine
CSF	Cerebrospinal fluid
CVA	Cerebrovascular accident
5,7-DHT	5,7-Dihydroxytryptamine
DOI	1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane 1-(2,5-Dimethoxy-4-iodoamphetamine)
DRN	Dorsal raphé nucleus
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders (3rd Edition: revised)
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
DUAG	Danish University Antidepressant Group
FDA	Federal Drug Administration
FDG	[^{18}F] Flurodeoxyglucose
FTI	Fatal Toxicity Index
GABA	γ-Aminobutyric acid
GAD	Generalized anxiety disorder
GH	Growth hormone
GTS	Gilles de la Tourette syndrome
HAM-A	Hamilton rating scale for anxiety
HAM-D	Hamilton rating scale for depression
5-HIAA	5-Hydroyindoleacetic acid
5-HT	5-Hydroxytryptamine
5-HTP	5-Hydroxytryptophan
8-OH-DPAT	8-Hydroxy-2-(di-*n*-propylamino)tetralin
HVA	Homovanillic acid
i.p.	Intraperitoneal
LLPDD	Late luteal phase dysphoric disorder
LOI	Leyton Obsessional Inventory
LSD	Lysergic acid diethylamide
MADRS	Montgomery-Asberg depression rating scale
MAO	Monoamine oxidase
MAOI(s)	Monoamine oxidase inhibitor(s)
*m*CPP	m-Chlorophenylpiperazine

MDD	Major depressive disorder
MDMA	3,4-Methylenedioxymethamphetamine
5-MeODMT	5-Methoxy-*N*,*N*-dimethyltrypamine
MHPG	3-Methoxy-4-hydroxyphenyl glycol
MMSE	Mini Mental State Examination
MRN	Median raphé nucleus
OCB	Obsessive-compulsive behaviors
OCD	Obsessive-compulsive disorder
OCS	Obsessive-compulsive symptoms
*p*CPA	*p*-*C*hlorophenylalanine
8-OH-DPAT	8-Hydroxy-2-(di-*n*-propylamino)-tetralin
PAG	Periaqueductal gray
PDR	Physician's Desk Reference (database)
PET	Positron emission tomography
PMDD	Premenstrual dysphoric disorder
PMS	Premenstrual syndrome
POA	Preoptic area (of the hypothalamus)
PRL	Prolactin
PTSD	Post-traumatic stress disorder
rCBF	Regional cerebral blood flow
REMS	Rapid-eye-movement sleep
RR	Relative risk (ratio)
SDAT	Senile dementia of Alzheimer's type
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone
SNRI	Serotonin noradrenaline reuptake inhibitor
SPECT	Single-photon emission computerized tomography
SSRI	Selective serotonin reuptake inhibitor
TCA(s)	Tricyclic antidepressant(s)
TD	Tardive dyskinesia
TRH	Thyrotropin-releasing hormone
TRP	Tryptophan
TS	Tourette's syndrome
VMN	Ventromedial nucleus (of the hypothalamus)
VTA	Ventral tegmental area (of the hypothalamus)
Y-BOCS	Yale-Brown obsessive-compulsive scale

CHAPTER 1

The Discovery of The SSRIs: A Milestone In Neuropsychopharmacology and Rational Drug Design

Arvid Carlsson

Besides being a major therapeutic advance, the selective serotonin reuptake inhibitors (SSRIs) have become important tools in basic and clinical brain research. They were the first drugs to establish beyond doubt a pathophysiological role for serotonin (5-HT) in affective illnesses and in the broad spectrum of anxiety disorders. Likewise, the SSRIs were the first to confirm the inhibition of neurotransmitter reuptake as an important therapeutic principle. As a result, the discovery of these agents marks a milestone in neuropsychopharmacology and rational drug design. Below is an account of the fascinating, winding path of research leading to the SSRIs.

The antidepressant action of imipramine was discovered in 1957 by Kuhn.[1] At first pharmacologists were taken aback because this action was entirely unpredicted. In 1959 Sigg[2] demonstrated that imipramine can potentiate the effects of noradrenaline as well as the response to sympathetic nerve stimulation. This was the first clue to the elucidation of the mode of action of imipramine. In 1960 Burn and Rand[3] described the uptake of noradrenaline by adrenergic nerves. Cocaine was reported to block this uptake. In the same year, Marshall et al[4] reported that the uptake of 5-HT by platelets could be blocked by imipramine and, in 1961, Axelrod et al[5] described the uptake of labeled noradrenaline by adrenergic nerves. This uptake could be blocked by imipramine, cocaine and reserpine. At the same time Dengler et al[6] reported similar data regarding noradrenaline uptake by brain tissue.

Disentangling the Riddle of Dual Amine Transport

These observations were of course interesting but did not lend themselves easily to interpretation. Particularly confusing was Axelrod's finding[5] that drugs with entirely different pharmacological profiles, i.e., imipramine and reserpine, seemed to have the same effect on the uptake of noradrenaline. This enigma was resolved by the discovery that amine-storing cells are equipped with two distinct amine-concentrating mechanisms. One of these is localized on the cell membrane and is sensitive to imipramine while the other is found on the membranes of intracellular vesicles (or granules) and blocked by reserpine. Blockade of the cell membrane pump leads to enhanced neurotransmission, whereas blockade of the

Selective Serotonin Reuptake Inhibitors (SSRIs): Past, Present and Future,
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intracellular mechanism causes failure of neurotransmission via depletion of neurotransmitter. As briefly summarized below, some of the early work leading to this discovery dealt partly with the storage of 5-HT by platelets and partly with the corresponding mechanisms in catecholamine-storing cells.

An early important discovery was that adrenal medullary cells are capable of storing catecholamines in special organelles, called granules or vesicles.[7,8] Subsequently, similar organelles were found to exist in adrenergic neurons, especially in their nerve terminals. The first observation of a specific drug effect on amine storage was reported by Brodie and his colleagues[9] who showed that reserpine is capable of depleting the tissue store of 5-HT: this effect was shown to be exerted directly on the platelet 5-HT stores by low concentrations of reserpine added in vitro.[10] Soon afterwards a similar action of reserpine on the storage of catecholamines was discovered.[11,12]

The first clue that the site of action of reserpine was at the subcellular level came from experiments on isolated adrenal medullary granules. These were found to take up labeled monoamines in vitro provided that adenosine triphosphate (ATP) was present.[13,14,15] This uptake could be blocked by low concentrations of reserpine but not by imipramine. Subsequent experiments using histochemical techniques demonstrated the imipramine-sensitive, reserpine-resistant amine uptake by the cell membranes of adrenergic nerves[16] (see also: ref. 17). Initially there was some controversy regarding this dual mechanism. For example, Brodie and his colleagues[18] maintained an opposite view, namely that reserpine acted on the amine uptake located on the cell membrane whereas imipramine acted on vesicular uptake. It was not long, however, until the former alternative was generally accepted. Recently, the different types of transporter protein have been cloned (Chapter 10).

The Tricyclic Antidepressants and the Amine Uptake Theory

As early as the 1960s, a sufficient body of evidence seemed to exist to formulate the hypothesis that the antidepressant action of imipramine and related tricyclic antidepressants was due to blockade of amine reuptake, leading to an increased aminergic neurotransmission. However, there were some caveats. In fact, several kinds of objections were raised but, in my opinion, some of these did not carry much weight. For example, concern was raised about the slow onset of antidepressant effect compared with the almost immediate blockade of amine uptake. However, given the powerful adaptive capacity of the brain, it is not hard to envisage that an originally distinct change, induced by a drug or a pathological process, could lead to a complex cascade of secondary changes in various neurocircuits. These changes could take weeks or even months to evolve and outlast considerably the presence of the drug or initial disturbance.

More serious was the objection dealing with the complex pharmacology of the tricyclic antidepressant drugs. Besides blocking amine reuptake they have affinity for a large number of receptors (e.g., cholinergic, adrenergic, histaminergic) and in addition they have a relatively strong so-called membrane-stabilizing action which leads to cardiotoxicity, lowering of seizure threshold etc. To exclude a role for these various mechanisms in the antidepressant action proved difficult. In fact, the general opinion in the scientific community was probably adequately expressed in Goodman and Gilman's textbook, as late as 1980 (Sixth edition),[19] when they commented that there is increasing doubt that the monoamine uptake theory is "either a necessary or sufficient explanation of the antidepressant action of these drugs." In subsequent editions, this comment has been deleted and opinion has shifted in favor of the amine uptake theory. Below an account will be given of the developments leading to this shift.

5-HT Enters the Scene

In the late 1960s, those who believed in the monoamine-uptake theory focused on the reuptake of noradrenaline. In fact, before 1968 there was no evidence that any other amine was involved in the action of the tricyclic antidepressants insofar as uptake inhibition is concerned. The early report referred to above on the action of imipramine on 5-HT uptake by platelets[4] seemed to have been completely forgotten.

However, in 1968 Carlsson, Fuxe and Ungerstedt[20] reported that the reuptake of 5-HT by central serotonergic neurons was blocked by imipramine. Subsequent work on a large number of tricyclic antidepressants showed that they are able to block the amine-uptake mechanism both in noradrenergic and serotonergic neurons but that there are considerable differences in potency among these agents with respect to their effects on these two types of neuron. Thus, among the tricyclics, the secondary amines were generally more potent than tertiary amines in terms of inhibiting noradrenaline uptake, whereas the reverse was true for inhibition of 5-HT uptake.[21,22]

Clomipramine was an especially potent inhibitor of 5-HT reuptake but, at this time, had not yet been tested in clinical trials. We were impressed by the marked differences in profile among the tricyclic antidepressants and so I visited Geigy in 1968 to report on our findings and urged Geigy to test this agent in the clinic. Unfortunately, Geigy had already decided in favor of another tricyclic agent. However, that agent turned out to possess some (probably toxicological) problems. As a result, clomipramine was then selected for clinical trials and the peculiar clinical profile of this compound was thus discovered.

Development of the First SSRI: Zimelidine

Even before the introduction of clomipramine into the clinic, our research group had proceeded with attempts to develop a 5-HT-selective reuptake inhibitor. We discovered a number of non-tricyclic agents with amine-uptake inhibitory properties, acting on both noradrenergic and serotonergic neurons. Some of these agents were found among the addictive analgesics, e.g., pethidine, while others were antihistamines.[23] Especially potent among the latter were pheniramine and its bromine- and chlorine-substituted derivatives as well as diphenhydramine.

Together with the skillful Swiss organic chemist Dr. Hans Corrodi, who at that time was employed by Hässle (a subsidiary of Astra) but later was promoted to Director of Research at Astra, I decided to start out from brompheniramine in an attempt to develop a selective serotonin (5-HT) reuptake inhibitor. We made and tested zimelidine which proved to be the first SSRI and was patented[24] with the priority date April 28, 1971; the publication date of the first (Belgian) patent was March 23, 1972.

Corrodi was eager to delay the publication of our data except, of course, for patents. In fact, these data were extensively published only in the patents because Corrodi prematurely died of a fulminant leukemia early in 1974. The subsequent publication by Astra scientists on the preclinical properties of zimelidine[25] referred to these patents and provided additional data to support the contention that zimelidine is an SSRI.

Regarding the clinical development of zimelidine, a phase I study was completed in 1971 at Hässle. Thereafter, the project was transferred to Astra Läkemedel at Södertälje, Sweden. The first open study of zimelidine in patients suffering from depression was published in 1976.[26] In April 1980, a symposium entitled 'Recent Advances in the Treatment of Depression' was held in Corfu, Greece.[27] In his concluding remarks Dr. Linford Rees, referring to several well-controlled clinical trials, concluded that zimelidine "is as effective as existing antidepressants in treating depression and in reducing anxiety, yet having a much lower incidence of those side-effects which are known to be particularly troublesome with the conventional tricyclic antidepressants." Zimelidine was approved in Sweden and several

other countries as an antidepressant agent in 1982 and soon became extensively used in those markets where it was available.

After more than 200,000 patients had been treated with zimelidine, in most cases with satisfactory or even excellent results, it became apparent that this SSRI could induce a serious, though generally not lethal, side-effect (Guillain-Barré syndrome) in a few patients. After treatment of at most 80,000 patients with zimelidine in Sweden, 8 cases of this syndrome were identified. It was estimated that at least 1 out of 10,000 patients treated with zimelidine would exhibit this syndrome, compared to the apparently spontaneous occurrence of this syndrome in 1 out of 50,000 individuals. This difference was statistically significant and the drug was withdrawn from the market in all countries on September 17, 1983. However, because of its outstanding therapeutic properties, zimelidine continued to be used 'on license' in Sweden for several years by thousands of patients. In fact, according to Dr. Jan Wålinder, who has considerable experience with zimelidine treatment, there is no risk of serious side-effects provided that the doctor watches for signs of supersensitivity to this drug. Wålinder maintains that the withdrawal of zimelidine was a mistake (for a detailed account, see ref. 28, authored by Dr. Ivan Östholm, at that time Director of Research at Hässle).

Fluoxetine and Other SSRIs

The development of fluoxetine has been described in a minireview in *Life Sciences*,[29] entitled 'Prozac (Fluoxetine, Lilly 110140), the First Selective 5-HT Uptake Inhibitor and an Antidepressant Drug.' As detailed below, however, fluoxetine was clearly preceded by zimelidine. Moreover, as acknowledged by the Lilly scientists,[30] the development of fluoxetine was based on concepts developed by our research group and started from our discovery that diphenhydramine has 5-HT- and noradrenaline-reuptake inhibitory properties. Fluoxetine has a chemical structure closely related to diphenhydramine. This was analogous to the development of zimelidine, starting out from the pheniramines. In addition, the in vivo and in vitro methodology used in the development of fluoxetine was similar to that developed by our research group.

The first experiment with fluoxetine, demonstrating 5-HT reuptake inhibitory properties, was performed in Dr. David Wong's laboratory on May 8, 1972. On July 24 of the same year, fluoxetine was recognized as the most potent and selective inhibitor of 5-HT reuptake among its congeners. These events thus took place more than a year after the priority date of the zimelidine patent and more than one month after the first zimelidine patent was published. The first patent application including fluoxetine was filed in late 1973, i.e., more than two years after the priority date of the zimelidine patent. The first publication on fluoxetine, demonstrating its SSRI profile, appeared in 1974,[30] more than two years after the first patent on zimelidine became public. It is hard to believe that the zimelidine patents did not become known shortly after their publication to drug-company scientists working in the same area. In any event these patents were noted in reference 25, which was quoted by Wong et al.[29]

Regarding the clinical development of fluoxetine, an Investigational New Drug Application was filed with the FDA in 1976, i.e., the same year as the first open phase II study with zimelidine was published.[26] After successful clinical studies with the drug, a New Drug Application for fluoxetine was filed with the Federal Drug Administration (FDA) in 1983. It was approved for marketing in 1987, i.e., 5 years after the approval of zimelidine in several European countries. It was introduced for clinical use in January 1988 so the clinical phase of the development of fluoxetine was slower than that of zimelidine. In retrospect, a somewhat slower and more careful clinical development of zimelidine might have changed the fate of this drug; the recommended doses were probably too high, as suggested by two early studies,[31,32] and there were indications that the risk of developing Guillain-Barré

syndrome was dose-dependent. As will appear from a note jointly authored by Dr. Wong and myself[33] there is at present no disagreement between us concerning the essential aspects of the early history of the SSRIs.

Zimelidine and fluoxetine were later followed by several SSRIs which are now on the market. As will be apparent from the following chapters of this book, this novel group of agents has had a great impact on both basic brain research and clinical psychiatry. Concerning one of these subsequent SSRIs, citalopram, our research group has been somewhat involved at an early stage. We studied a series of bicyclic compounds developed by Lundbeck and were able to confirm a finding of the Lundbeck scientists: that these agents are potent inhibitors of noradrenaline reuptake but we found that these agents had no significant effect on 5-HT reuptake.[34] We then reported to the Lundbeck scientists that a noradrenaline-selective drug can be converted into a drug with a greater affinity for 5-HT reuptake by increasing the lipophilicity of the molecule through appropriate substitutions. Citalopram appears to be a modification of the bicyclic compounds studied by us in this direction.

Conclusion

It should be noted that zimelidine, fluoxetine and several other SSRIs are selective not only in regard to inhibition of 5-HT reuptake compared with that of catecholamines but also in that, unlike tricyclic antidepressants, they lack affinity for a number of receptors and have no 'membrane-stabilizing' action leading to cardiotoxicity and lowered seizure thresholds. Thus, for the first time, inhibition of monoamine uptake was confirmed as an important therapeutic principle.

Looking back, it is fair to say that the research leading to the therapeutic principle of selective 5-HT reuptake inhibition marks a milestone in the history of neuropsychopharmacology and rational drug development. Sadly, the premature death of Dr. Hans Corrodi, one of the foremost pioneers in this endeavor, deprived him of the satisfaction of witnessing how his achievements contributed to a major scientific and therapeutic advance which has benefited millions of patients.

References

1. Kuhn R. The treatment of depressive states with G22355 (imipramine hydrochloride). Am J Psychiatry 1958; 115:459.
2. Sigg EB. Pharmacological studies with tofranil. Canad Psychiatric Ass J 1959; 45:75-85.
3. Burn JH. Tyramine and other amines as noradrenaline-releasing substances. In: Vane JR, Wolstenholme GEW, O'Connor M, eds. Ciba Foundation Symposium on Adrenergic Mechanisms. London: J & A Churchill Ltd., 1960:326-336.
4. Marshall E, Stirling GS, Tait AC et al. The effect of iproniazid and imipramine on the blood platelet serotonin in man. Br J Pharmacol 1960; 15:35-41.
5. Axelrod J, Whitby LG, Hertting G. The effect of psychotropic drugs on the uptake of ^{3}H-norepinephrine by tissues. Science 1961; 133:383-384.
6. Dengler HJ, Spiegel HE, Titus EO. Uptake of tritium-labeled norepinephrine in brain and other tissues of cat in vitro. Science 1961; 133:1072-1073.
7. Hillarp N-Å, Lagerstedt S, Nilson B. The isolation of a granular fraction from the suprarenal medulla containing the sympathomimetic catecholamines. Acta Physiol Scand 1953; 28:251-263.
8. Blaschko H, Welch AD. Localization of adrenaline in cytoplasmic particles of the bovine adrenal medulla. Naunyn-Schmiedeberg's Arch Exp Path Pharmak 1953; 219:17-22.
9. Pletscher A, Shore PA, Brodie BB. Serotonin release as a possible mechanism of reserpine action. Science 1955; 122:374-375.
10. Carlsson A, Shore PA, Brodie BB. Release of serotonin from blood platelets by reserpine in vitro. J Pharm Exp Ther 1957; 120:334-339.

11. Bertler Å, Carlsson A, Rosengren E. Release by reserpine of catecholamines from rabbits' hearts. Naturwissenschaften 1956; 22:521.
12. Carlsson A, Bertler Å, Rosengren E et al. Effect of reserpine on the metabolism of catecholamines. In: Garattini S, Ghetti V, eds. Psychotropic Drugs. Amsterdam: Elsevier, 1957:363-372.
13. Carlsson A, Hillarp N-Å, Waldeck B. A Mg^{++}-ATP-dependent storage mechanism in the amine granules of the adrenal medulla. Med Exp (Basel) 1962; 6:47-53.
14. Carlsson A, Hillarp N-Å, Waldeck B. Analysis of the Mg^{++}-ATP-dependent storage mechanism in the amine granules of the adrenal medulla. Acta Physiol Scand 1963; 59(suppl 215):1-38.
15. Kirshner N. Uptake of catecholamines by a particulate fraction of the adrenal medulla. J Biol Chem 1962; 237:2311-2317.
16. Malmfors T. Studies on Adrenergic Nerves. The use of rat and mouse iris for direct observations on their physiology and pharmacology at cellular and subcellular levels. Acta Physiol Scand 1965; 248(Suppl):64.
17. Carlsson A. Physiological and pharmacological release of monoamines in the central nervous system. In: von Euler US, Rosell S, Uvnäs B, eds. Mechanisms of Release of Biogenic Amines. Oxford: Pergamon Press, 1966:331-346.
18. Costa E, Gessa GL, Kuntzman R et al. The effect of drugs on the storage and release of serotonin and catecholamines in brain. In: Paton WDM, Lindgren P, eds. Pharmacological Analysis of Central Nervous Action. Oxford: Pergamon Press, 1962:43-71.
19. Goodman LS, Gilman A., eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 6th ed. New York: MacMillan, 1980:420.
20. Carlsson A, Fuxe K, Ungerstedt U. The effect of imipramine on central 5-hydroxytryptamine neurons. J Pharm Pharmacol 1968; 20:150-151.
21. Carlsson, Corrodi H, Fuxe K et al. Effects of some antidepressant drugs on the depletion of brain catecholamine stores caused by 4-α-dimethyl-metatyramine. Eur J Pharmacol 1969; 5:367-373.
22. Carlsson A, Corrodi H, Fuxe K et al. Effects of some antidepressant drugs on the depletion of brain 5-hydroxytryptamine stores caused by 4-methyl-α-ethyl-metatyramine. Eur J Pharmacol 1969; 5:357-366.
23. Carlsson A, Lindqvist M. Central and peripheral membrane pump blockade by some addictive analgesics and antihistamines. J Pharm Pharmacol 1969; 21:460-464.
24. Berntsson PB, Carlsson PAE, Corrodi HR. Composés utiles en tant qu'agents anti-dépressifs, et procédé pour leur préparation. Belg Pat No 1972; 781:105.
25. Ross SB, Ögren SO, Renuy AL. (Z)Dimethylamino-1-(4-bromophenyl)-1-(3-pyridyl)propene (H102/09), a new selective inhibitor of the neuronal 5-hydroxytryptamine uptake. Acta Pharmacol Toxicol 1976; 39:152-166.
26. Siwers B, Ringberger V-A, Tuck JR et al. Initial clinical trial based on biochemical methodology of zimelidine (a serotonin uptake inhibitor) in depressed patients. Clin Pharmacol Ther 1977; 21:194-200.
27. Carlsson A, Gottfries C-G, Holmberg G et al. Recent Advances in the Treatment of Depression. Acta Psychiatr Scand 1981; 63(Suppl. 290):1-477.
28. Östholm I. Drug Discovery—A Pharmacist's Story. Stockholm: Swedish Pharmaceutical Press, 1995:108.
29. Wong DT, Bymaster FP, Engleman EA. Prozac (Fluoxetine, Lilly 110140), the first selective serotonin uptake inhibitor and an antidepressant drug. Life Sci 1995; 57:411-441.
30. Wong DT, Horng JS, Bymaster FP et al. A selective inhibitor of serotonin uptake: Lilly 110140, 3-(p-trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine. Life Sci 1974; 15:471-479.
31. Wålinder J, Carlsson A, Persson R. 5-HT reuptake inhibitors plus tryptophan in endogenous depression. Acta Psychiatr Scand 1981; 290(Suppl):179-199.
32. Montgomery SA, McAuley R, Rani SJ et al. A double blind comparison of zimelidine and amitriptyline in endogenous depression. Acta Psychiatr Scand 1982; 290(Suppl):314-327.

33. Carlsson A, Wong DT. Correction: A note on the discovery of selective serotonin reuptake inhibitors. Life Sci 1977; 61:1203.
34. Carlsson A, Fuxe K, Hamberger B et al. Effect of a new series of bicyclic compounds with potential thymoleptic properties on the reserpine-resistant uptake mechanism of central and peripheral monoamine neurons in vivo and in vitro. Br J Pharmacol 1969; 36:18-28.

Chapter 2

Clinical Pharmacokinetics of SSRIs

Pierre Baumann, Chin B Eap and Pierre Voirol

Citalopram,[1] fluoxetine,[2,3] fluvoxamine,[4] paroxetine[5] and sertraline[6] are the five antidepressants which are known as selective serotonin reuptake inhibitors (SSRIs) (Fig. 2.1). Their clinical efficacy, good tolerance and safety have been demonstrated in many studies[7,8] and some of them may also be prescribed successfully for the treatment of obsessive compulsive disorder, bulimia or panic attacks. Despite their common pharmacological properties, the SSRIs differ in their metabolism by cytochrome P450 and in their interaction profile with other drugs which are also substrates of this enzyme system. Sensitive and selective (including stereoselective) methods, using high performance liquid chromatography or gas chromatography, have been introduced for their quantitative analysis in blood samples.[9] These have enabled studies of their pharmacokinetics as well as investigations of the relationship between plasma concentration and clinical efficacy. This review summarizes our present knowledge of the metabolism, pharmacokinetics and pharmacogenetics of this group of antidepressants.

Metabolism and Pharmacokinetic Properties of SSRIs

The SSRIs differ widely in their chemical structure (Fig. 2.1) which explains the differences in their pharmacological profile regarding inhibition of serotonin (5-hydroxytryptamine, 5-HT) and noradrenaline uptake by nerve endings. Fluoxetine and citalopram are produced commercially as racemates. Figure 2.2 shows that uptake inhibition of both 5-HT and noradrenaline displays stereoselectivity when the chiral compounds citalopram and fluoxetine and their metabolites are considered.[10] Citalopram and fluoxetine have active metabolites but, most probably, only norfluoxetine has to be considered as a clinically relevant metabolite. Sertraline is the most potent 5-HT uptake inhibitor, and S-citalopram is the most selective of these agents with regard to 5-HT as compared to noradrenaline uptake inhibition. SSRIs also present some interindividual differences with regard to their affinity for adrenergic, muscarinic, histaminic and serotonergic receptors as well as for 5-HT and noradrenaline transporters,[11,12] but data are scarce regarding these properties for the enantiomers of the chiral SSRIs.

Cytochrome P450 of the liver contributes, to a large extent, to the metabolism of SSRIs but the role of the isozymes implicated in this process varies considerably from one compound to another.

As summarized in Table 2.1, a genetic polymorphism has been described for two of these cytochromes, CYP2D6 and CYP2C19. Patients who, for genetic reasons, are unable to metabolize substrates of these enzymes undergo a higher risk of adverse effects when treated with such drugs.[13] In the case of CYP2D6, gene amplification has been demonstrated which explains the existence of ultrarapid metabolizers.[14,15] Debrisoquine, sparteine and dextromethorphan are the drugs which are commonly used for CYP2D6 phenotyping.

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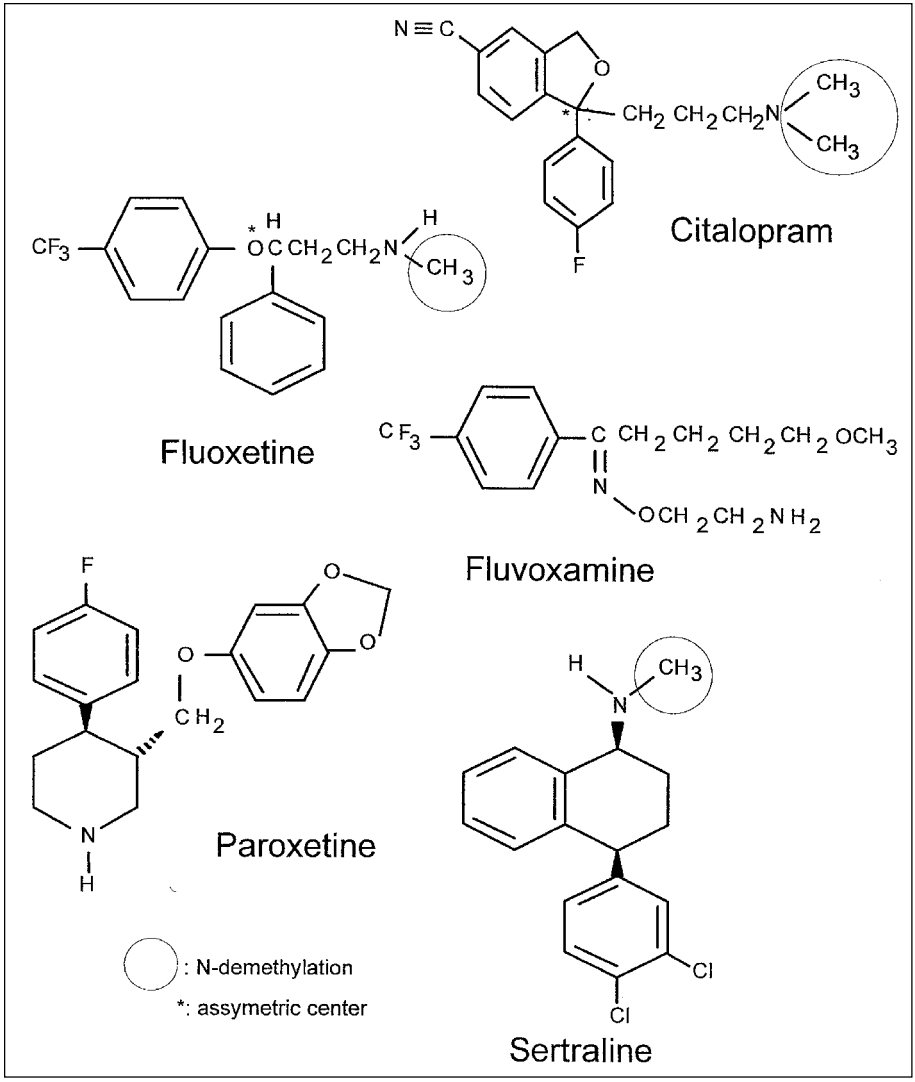

Fig. 2.1. Chemical formulae and N-demethylation pathway of SSRIs.

Caffeine, mephenytoin and dextromethorphan (or midazolam) are used as test probes for measuring CYP1A2, CYP2C19 and CYP3A4 activity, respectively. Subjects may be genotyped for CYP2D6 or CYP2C19 with appropriate molecular biological techniques.[13,16] There is a high interindividual variability in the activity of CYP1A2 and CYP3A4. Furthermore, these enzymes can be induced by exogenous factors, such as tobacco smoke (CYP1A2) and drugs like carbamazepine and barbiturates (CYP3A4) (Table 2.1). CYP1A2, CYP2D6, CYP2C19, CYP3A4, and possibly CYP2C9, are the main enzymes involved in the metabolism of SSRIs, albeit to variable degrees (Fig. 2.3).

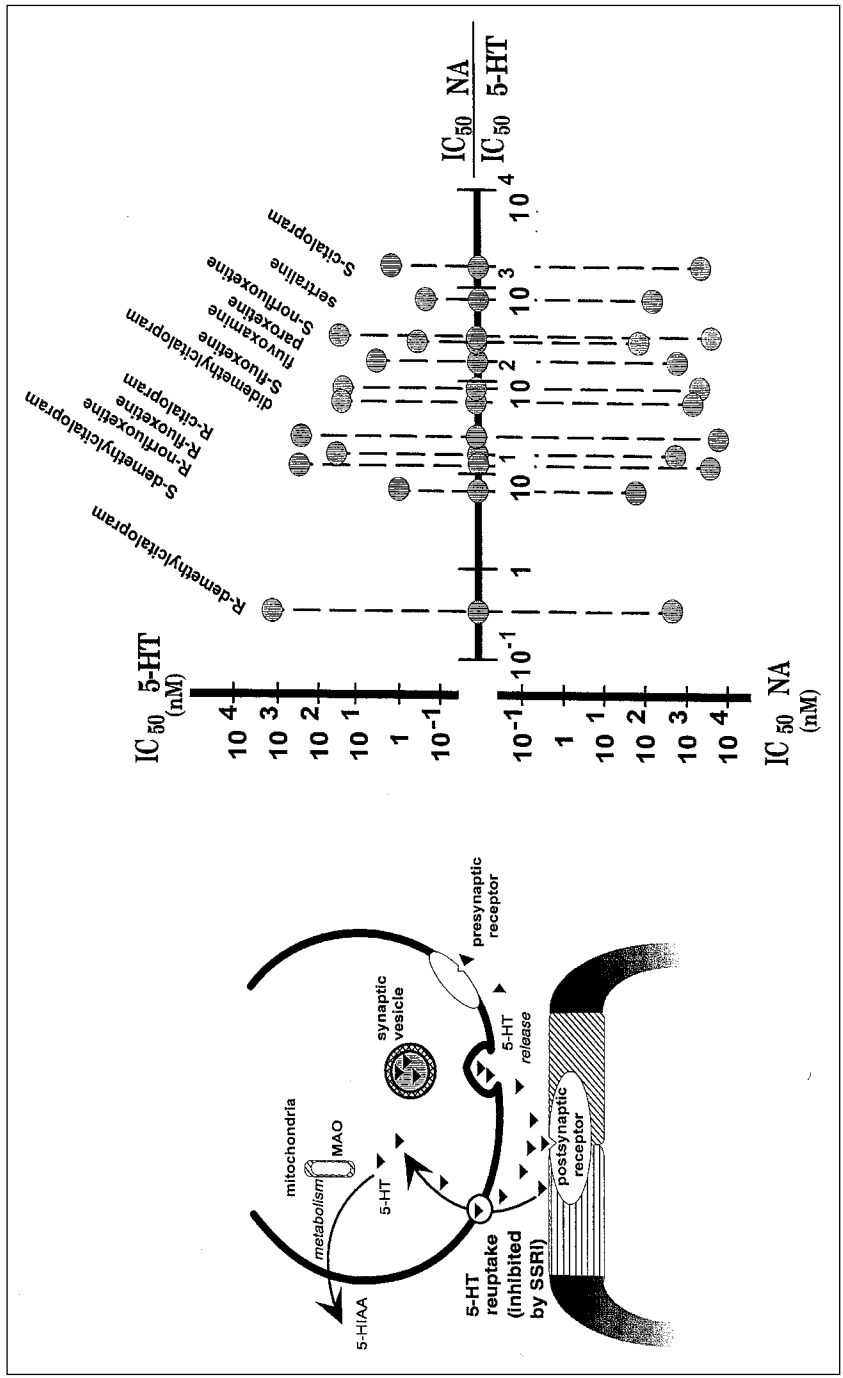

Fig. 2.2. 5-HT and noradrenaline reuptake inhibition properties of SSRIs at the synaptic level (as described by Baumann and Rochat, 1995).[10]

Table 2.1. Properties of cytochrome P450 isozymes involved in the metabolism of SSRIs and/or inhibited by SSRIs

Isoenzyme	Genetic polymorphism	% Poor metabolizers (Europe)	Isozyme inducible	Typical substrates	Typical inhibitors
CYP1A2	no	-	yes (tobacco-smoke)	caffeine clozapine	fluvoxamine
CYP2C9	yes	rare	yes (anticonvulsants)	phenytoin	sulfaphenazole
CYP2C19	yes	3-5	no (?)	mephenytoin diazepam	omeprazol
CYP2D6	yes	5-10 (*)	no	dextromethorphan debrisoquin, sparteine	thioridazine quinidine
CYP3A4	no	-	yes (carbamazepine)	triazolam	erythromycine

(*): also ultrarapid metabolizers (1-7 % of the population) (gene amplification)

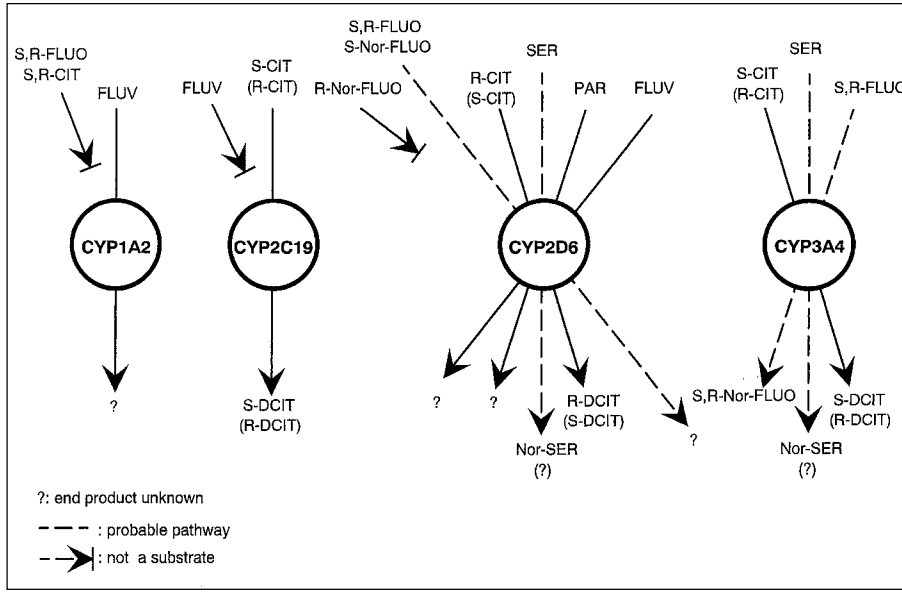

Fig. 2.3. Role of cytochrome P450 isozymes in the biotransformation of SSRIs. CIT: citalopram; DCIT demethylcitalopram; FLUO: fluoxetine; FLUV: fluvoxamine; PAR: paroxetine; SER: sertraline.

There is now evidence that racemic fluoxetine is *N*-demethylated to norfluoxetine[17] and sertraline to norsertraline[18] by CYP2C9 in vitro. The role of this enzyme in the metabolism of these and other SSRIs remains to be clarified but it is actually inhibited by some of these compounds.[19] As shown in Figure 2.3, the limitations of our present knowledge are striking. This is particularly the case when considering the nature of the most important metabolites of SSRIs as well as the exact mechanisms or enzymes leading to their formation. Several review papers have recently been published on the metabolism and pharmacokinetics of the SSRIs (Table 2.2).[20-23]

Citalopram

Citalopram is a tertiary amine (Fig. 2.1) which is N-demethylated to demethylcitalopram and didemethylcitalopram. These metabolites are also SSRIs but plasma concentrations of N-didemethylcitalopram are extremely low in clinical conditions. Recently, we have shown that the propionic acid derivative of citalopram, an inactive metabolite, is formed by the enzyme, monoamine oxidase (MAO; see below).[36] The S-enantiomers of citalopram and the N-demethylated metabolites are more potent than the R-enantiomers in inhibiting 5-HT reuptake (Fig. 2.2).[37] Taking account of the plasma concentrations observed in clinical conditions, S-citalopram has therefore to be considered as the pharmacologically relevant compound.[38,39]

The first in vivo studies on the role of cytochrome P450 in the metabolism of citalopram produced evidence for control of N-demethylation of racemic citalopram and demethylcitalopram by CYP2C19 and CYP2D6, respectively (Fig. 2.3).[40] In studies of human liver microsomes and cytochrome P450 isozymes expressed by cDNA in human B-lympho-blastoid cell lines in vitro, we demonstrated that the enantiomers of citalopram

Table 2.2. General comparative pharmacokinetics of SSRIs

SSRI Active metabolites	Cmax (ng/ml) (after mg single dose)	Tmax (h)	T1/2 (h) plasma	Vd (l/kg)	Bio-availability (%)	Free fraction (%)	Cl/F (ml/min)	References
Citalopram Demethylcitalopram Didemethylcitalopram	39(40)	2-4	(23-75) 33 ± 7 51.7 ± 8.0 (a) 101.1 ± 23.1 (a)	12-16	80	20	378 ± 65	24-26
Fluoxetine Norfluoxetine	15-55 (30 or 40)	6-8	1-4 7-15	12-43 11-88	ca 70	5.5	94-703	27-28
Fluvoxamine	14 ± 4 (50) (b)	7.8 ± 2.4 (b)	11.7 ± 3.0 (b)	5	53	23	3000 ± 1200 (b)	29-30
Paroxetine	10.7 ± 10.4 (20)	5.8 ± 1.7	7-65	8-28	ca 50	5	1230-7720 (c)	31-34
Sertraline Norsertraline	118 ± 22 (m); 166 ± 65 (f); 200 (*) 156 ± 36 (m); 244 ± 80 (f)	6.9 ± 1.0 (m) 6.7 ± 1.8 (f) 9.1 ± 3.0 (m); 5.9 ± 3.1 (f)	22.4 (m) 32.1 (f) 79	>20		1.5	23.5 ± 6 (m); 22.5 ± 11.1 (f)**	35 and Pfizer, data on file

Data, if available, are presented as means ± s.d. or ranges: d (days) m (male), f (female)
(a): in subjects co-medicated with cimetidine (ref. 26); (b): in 10 extensive metabolizers of dextromethorphan and non-smokers (ref. 29); (c) (ref. 34); *: after 30 days of treatment; ** ml/min/kg.

Table 2.3. Comparative pharmacokinetics of the chiral SSRIs citalopram and fluoxetine in phenotyped (CYP2D6) healthy subjects

	T1/2 (h) in plasma (a)		
SSRI	**EMs**	**PMs**	**References**
S-citalopram	34.8 ± 4.3*		39
R-citalopram	46.9 ± 10.6		
S-demethylcitalopram	50.6 ± 12.7*		
R-demethylcitalopram	69.8 ± 18.8		
S-fluoxetine	26.7	147.1**	44-45
R-fluoxetine	63.5	227.6*	
S-norfluoxetine	131.8	417.6**	
R-norfluoxetine	132.9	166.3 n.s.	

(a) for citalopram, means ± s.d.; for fluoxetine, median values
Citalopram study, comparison S- versus R-enantiomers; *,P<0.05
Fluoxetine study, Mann-Whitney, EMs vers PMs; *,P<0.05; **,P<0.01
EMs and PMs, extensive and poor metabolizers of sparteine, respectively.

are stereoselectively *N*-demethylated. CYP2D6 preferentially *N*-demethylates R-citalopram but its role is minor in the overall metabolism by cytochrome P450. S-citalopram is preferentially metabolized by CYP3A4 and CYP2C19.[41] We observed that, in patients submitted to a citalopram treatment, the ratio of S/R-citalopram averages about 0.5 in plasma at steady-state conditions.[38,42,43] This ratio reaches unity in patients with a genetic deficiency of CYP2C19 (Baumann et al, in preparation).A pharmacokinetic study on the fate of the enantiomers of citalopram at steady-state conditions (Table 2.3) shows that, in extensive metabolizers of sparteine (CYP2D6) and mephenytoin (CYP2C19), the pharmacologically relevant enantiomer, S-citalopram, has a shorter plasma half-life than does R-citalopram.[39] This is probably explained by the fact that CYP2C19 preferentially demethylates S-citalopram.

Citalopram is the only SSRI available for intravenous treatment. In our study of the hormonal effects of an intravenous infusion of citalopram (20 mg) in healthy volunteers, the only measurable metabolite in plasma was its propionic acid derivative.[46] It has therefore to be considered as an important metabolite but, until recently, no data were available on the mechanism of its formation. Our in vitro studies with human liver suggest that MAO-A and MAO-B and aldehyde oxidase stereoselectively control the deamination of citalopram and its *N*-demethylated metabolites and that, in this respect, *N*-demethylcitalopram appears to be the best substrate.[36] The S-enantiomers are preferentially metabolized by MAO-B, and the R-enantiomers by MAO-A. The biotransformation of citalopram is strongly inhibited by the MAO-A inhibitor, clorgyline, and that of didemethylcitalopram by the MAO-B

inhibitor, selegiline. This seems to be the first demonstration that MAO is involved in the metabolism of psychotropic drugs which are used therapeutically. It remains to be demonstrated whether other drugs of this family are also metabolized by MAO but, for fluoxetine[47] and sertraline at least, deaminated metabolites have been described. With regard to its pharmacokinetic properties, and in comparison with other SSRIs, citalopram is the antidepressant with the highest bioavailability (about 80%) (Table 2.2). This explains why, in our comparative study of the clinical effectiveness of intravenous versus oral citalopram (40 mg/day) in depressive patients, the concentrations of citalopram in plasma at steady-state conditions did not differ between the two groups of patients.[49]

Fluoxetine

The secondary amine, fluoxetine, is *N*-demethylated to norfluoxetine (Fig. 2.3) which is also a potent and selective 5-HT uptake inhibitor. S- and R-fluoxetine and S-, but not R-norfluoxetine, have to be considered as SSRIs in view of their pharmacological profile (Fig. 2.2).[50,51] In clinical conditions, the ratio of S/R-fluoxetine varies from 0.93-3.63, and that of S/R norfluoxetine from 1.58-3.32.[52] The existence of a stereoselective metabolism of fluoxetine has been confirmed recently in that the R-enantiomers are more rapidly metabolized and eliminated than the corresponding S-enantiomers (Table 2.2). CYP2D6 contributes to the metabolism of fluoxetine and norfluoxetine, as shown in a panel study with healthy volunteers.[53] So far, it is unknown which pathway is concerned but it could be *O*-dealkylation.[47,54] We observed that, in poor metabolizers of sparteine (CYP2D6 deficiency), the elimination of S- and R-fluoxetine and of S-norfluoxetine, but not R-norfluoxetine, is impaired.[44,45] Possibly, in such patients, the occurrence of adverse effects may be more frequent: interestingly, an elderly depressive patient with a genetic deficiency of CYP2D6 has been described who suffered from a choreiform syndrome while treated with fluoxetine but no drug plasma concentrations were measured, unfortunately.[55] In vitro studies with racemic fluoxetine suggest that CYP2C9 is the main enzyme implicated in *N*-demethylation of fluoxetine to norfluoxetine while CYP2C19, CYP2D6 and CYP3A play a minor role. Fluoxetine does not seem to be metabolized by CYP1A2 (Fig. 2.3).[17]

Fluvoxamine

No active metabolite is known for the primary amine antidepressant, fluvoxamine. A panel study with healthy, non-smoking volunteers, previously phenotyped with dextromethorphan (CYP2D6) and mephenytoin (CYP2C19), suggests that CYP2D6 but not CYP2C19 plays some minor role in the metabolism of fluvoxamine.[29] CYP1A2, an enzyme induced by tobacco-smoking, could also contribute to the metabolism of fluvoxamine because elimination of fluvoxamine is more rapid in smokers than in non-smokers.[56] There is no direct evidence of the metabolites which are formed under the influence of cytochrome P450 (Fig. 2.3). Fluvoxamine is the SSRI with the shortest plasma half-life (Table 2.2).

Paroxetine

None of the metabolites of the secondary amine antidepressant, paroxetine,[5] seem to be active with regard to 5-HT uptake inhibition.[57] Paroxetine is transformed to hydroxylated metabolites and then glucuronidated. Catechol-*O*-methyltransferase (COMT) probably contributes to the formation of catechol metabolites. The metabolism of paroxetine is under the genetic control of CYP2D6, as shown in a panel study (Table 2.2).[33] This could explain the wide interindividual variability in the elimination kinetics of paroxetine. CYP2D6 could be involved in the oxidation of the methylenedioxyphenyl ring but direct evidence seems to be missing. Paroxetine displays non-linear kinetics, and probably other P450 isozymes contribute to its metabolism.[34]

Sertraline

Sertraline, a secondary amine (Fig. 2.1), is N-demethylated to the weakly active SSRI, norsertraline. Although the mechanism has not yet been clearly elucidated CYP3A4[53] and CYP2C9,[18] but not CYP2D6, are probably involved (Fig. 2.3). Another inactive metabolite is a ketone which could be formed by deamination (c.f., citalopram).[48]

Drug Blood Concentrations and Clinical Response

For none of the SSRIs has a plasma concentration—clinical effectiveness relationship been evinced.[23,58,59] Consequently, therapeutic monitoring is limited to indications such as: lack of compliance, non-response despite adequate doses, or the response in 'special populations' such as the elderly (see below). While, for most SSRIs, several studies have been carried out, none have been reported for the widely introduced sertraline. Also, only limited data have been published on the plasma concentrations of SSRIs in the clinical context.[23,60] Furthermore, there is a lack of published studies on the relationship between plasma concentration and clinical response to fluoxetine or citalopram which take account of their enantiomers. As reviewed recently,[61] pharmacokinetic studies have shown that in some 'special populations', SSRI doses should be modified. For instance, lower doses of citalopram, fluoxetine and sertraline should be used in patients suffering from liver disease. With paroxetine, a drug eliminated mainly by the kidney, the dose should be carefully adapted in patients suffering from renal disease. Finally, in elderly subjects, it is advisable to decrease the recommended doses of citalopram, paroxetine and sertraline but, generally, controlled studies of this group of patients are lacking.

Pharmacokinetic Interactions

The interest of clinical psychopharmacologists in cytochrome P450 arose more from the observation of pharmacokinetic interactions which involved the SSRIs and which had pharmacodynamic consequences than from the discovery of pharmacogenetic differences in the metabolism of psychotropic drugs. This interest was firstly centered on the role of CYP2D6, as this enzyme is inhibited in the interaction between fluoxetine and tricyclic antidepressants, an observation described in 1989.[62] For some drugs, this enzyme obviously plays an important role despite its relatively low abundance in the human liver compared with that of other CYP isozymes such as CYP3A, CYP2C9, CYP2C19 and CYP1A2 (Fig. 2.4).[63]

SSRIs can interact with CYP1A2, CYP2D6, CYP2C19 and CYP3A4 to a varying degree as reviewed by many authors (Fig. 2.4).[22,23,69-72] Only recently has CYP2C9 also been shown to be inhibited by some of these drugs.[19] This helps to explain the earlier, albeit inconsistently, observed pharmacokinetic interactions between some SSRIs and the CYP2C9 substrate, phenytoin.[73,74] The wide interindividual variability in the activity of these isozymes, together with the fact that most drugs are metabolized by several pathways involving one or several enzymes, explains some of the inconsistencies in these interactions. Moreover, plasma concentrations do not necessarily reflect drug levels in the brain yet the latter would probably correlate better with pharmacodynamic effects. For example, using [^{19}fluorine] magnetic resonance spectroscopy, it was recently shown that, in subjects treated with fluvoxamine, the mean elimination half-lives of fluvoxamine in brain and plasma were 58 h and 26 h, respectively.[75] This type of technique will therefore be an increasingly useful tool to ameliorate our lack of knowledge on the fate of SSRIs and other antidepressants in the target organ.

Citalopram can interact with cytochrome P450[76] to some extent. However, our case study with tricyclic antidepressants,[77] and other studies with neuroleptics, have shown that the clinical consequences of this interaction are minimal.[78] On the other hand, the recent demonstration that citalopram and its *N*-demethylated metabolites are substrates of MAO leads us to suspect clinical consequences after co-administration of these two types of

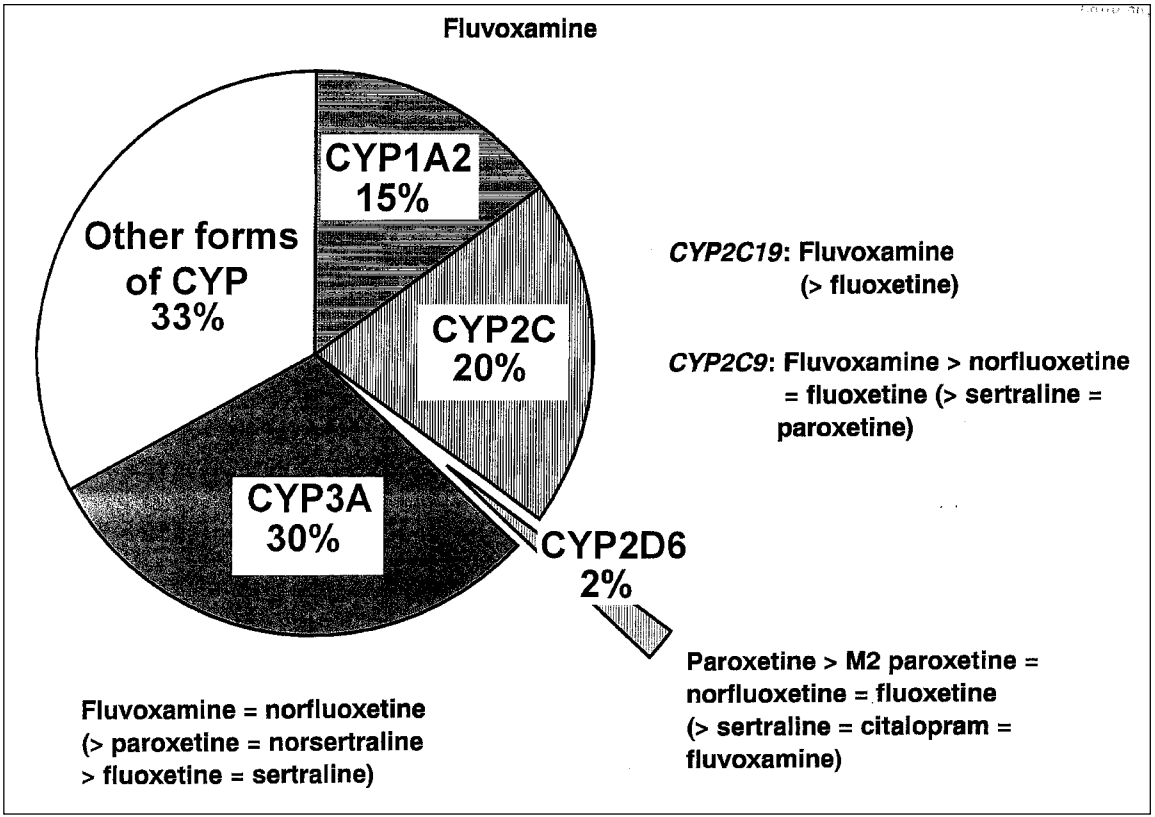

Fig.2.4. Relative abundance of cytochrome P450 isozymes in human liver and their inhibition by SSRIs.[63] The SSRIs are listed if there is a clinically relevant inhibition (SSRIs in parentheses: minor or moderate inhibition of no or little clinical significance).[19,64-68]

Table 2.4. Typical substrates of cytochrome P450, the metabolism of which may be inhibited by some SSRIs (c.f. Fig. 2.4.)

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Antipyrine	Diclofenac	Amitriptyline	Codeine	Alprazolam
Caffeine	Ibuprofen	Citalopram	Debrisoquine	Amiodarone
Clomipramine	Naproxen	Clomipramine	Dextromethorphan	Carbamazepine
Clozapine	Phenytoin	Diazepam	Flecainide	Citalopram
Imipramine	S-Warfarin	Imipramine	Fluoxetine	Clomipramine
Olanzapine	Tolbutamide	Mephaobarbital	Haloperidol	Cortisol
Paracetamol		Omeprazole	Maprotiline	Cyclosporin A
Phenacetine		Proguanil	Mianserin	Diazepam
S,R-Methadone		S-Mephenytoin	Mirtazapine	Erythromycin
Tacrine		Thioridazine	Paroxetine	Imipramine
Theophyline			Perphenazine	Midazolam
			Propafenone	Nifedipine
			Propranolol	Omeprazol
			R-Methadone	Quinidine
			Sertindol	S,R-Methadone
			Sparteine	Sertraline
			Thioridazine	Terfenadine
			Tramadole	Testosterone
			Tricyclic antidepressants	Triazolam
			Venlafaxine	Verapamil
			Zuclopenthixol	Zolpidem

drugs. Severe toxic effects have been described after overdoses of citalopram in the presence of moclobemide.[79] Nevertheless, a 10-day treatment of healthy volunteers with citalopram (20 mg/day) and the MAO-B inhibitor, selegiline (10 mg/day for 4 days) did not lead to any significant clinical problems. The selegiline treatment did not influence citalopram plasma concentrations but increased the area under the curve and C_{max} of demethylcitalopram as measured by an achiral method.[80] This finding is in line with our observation that, in vitro, MAO-B preferentially metabolizes this secondary amine rather than citalopram itself and that this reaction is inhibited by selegiline.[36] Unfortunately, the authors[80] did not measure either didemethylcitalopram or the propionic acid metabolite in their subjects.

Fluoxetine and norfluoxetine are known to be potent inhibitors of CYP2D6, an enzyme which contributes to the metabolism of many tricyclic antidepressants and other psychotropic drugs. In this respect, the S-enantiomers of fluoxetine and norfluoxetine display a similar potency. However, they are about 5-fold more potent than the corresponding R-enantiomers, as shown in studies of human liver microsomes in vitro.[10,81] Norfluoxetine, besides being a CYP2D6 inhibitor, also inhibits CYP3A4. Due to the long half-life of this metabolite this means that, even after withdrawal of fluoxetine, there is a long-lasting (several weeks!) risk of a pharmacokinetic interaction if treatment with another CYP3A4 substrate is initiated.

Because of its inhibition of CYP1A2, CYP2C9, CYP2C19 and, to a lesser extent, CYP2D6, fluvoxamine is considered to be a drug with a high potential for adverse interactions. This is especially the case with tricyclic antidepressants which are tertiary amines (e.g., imipramine, doxepin and amitriptyline) and with clozapine. However, in patients who are rapid metabolizers, due to genetic or environmental factors, coadministration of fluvoxamine with a tricyclic antidepressant[82,83] or clozapine,[84] a substrate of CYP1A2, can be beneficial.

The differential interaction profile of SSRIs is illustrated by the following study in which we compared the effects of fluoxetine and fluvoxamine, respectively, on the steady-state concentrations of the enantiomers of methadone.[85] Methadone seems to be a substrate of CYP2D6, CYP3A4 and CYP1A2 but it is stereoselectively metabolized. The exact mechanisms remain to be elucidated but R-methadone, which has to be considered as the pharmacologically active opioid enantiomer, could be preferentially metabolized by CYP2D6 whereas CYP1A2 apparently acts non-stereoselectively. Our study showed that, in methadone-treated patients comedicated with fluvoxamine (50-250 mg/day), the plasma concentrations of S-, R- and S,R-methadone were increased, while fluoxetine (20 mg/day) increased R-methadone only (Fig. 2.5).

Paroxetine and its metabolite, M2, are potent inhibitors of CYP2D6,[67] but studies of human liver microsomes in vitro initially showed conflicting results for sertraline (c.f. ref. 25). A recent clinical crossover study confirms that, in healthy volunteers treated with the CYP2D6 substrate desipramine, administration of paroxetine (20 mg/day for 10 days) leads to a more than 3-fold increase in desipramine plasma concentrations. However, the increase is less than 50% with sertraline (50 mg/day),[86] a result confirmed in similar studies.[87,88] The inference that paroxetine is a strong CYP2D6 inhibitor is strengthened by the finding that coadministration of paroxetine can increase plasma concentrations of perphenazine by as much as 2 to 13-fold and dramatically increase the side-effects of the latter drug in healthy volunteers.[89]

Another clinical interaction study with terfenadine, a CYP3A4 substrate, confirms that paroxetine has little effect on the kinetics of this H_1-receptor antagonist and therefore cannot be considered as a CYP3A4 inhibitor.[90] Preskorn et al[91] came to a similar conclusion using sertraline which also had little effect on the pharmacokinetics of the CYP3A4 substrates, terfenadine, carbamazepine or alprazolam. In subjects submitted to a caffeine

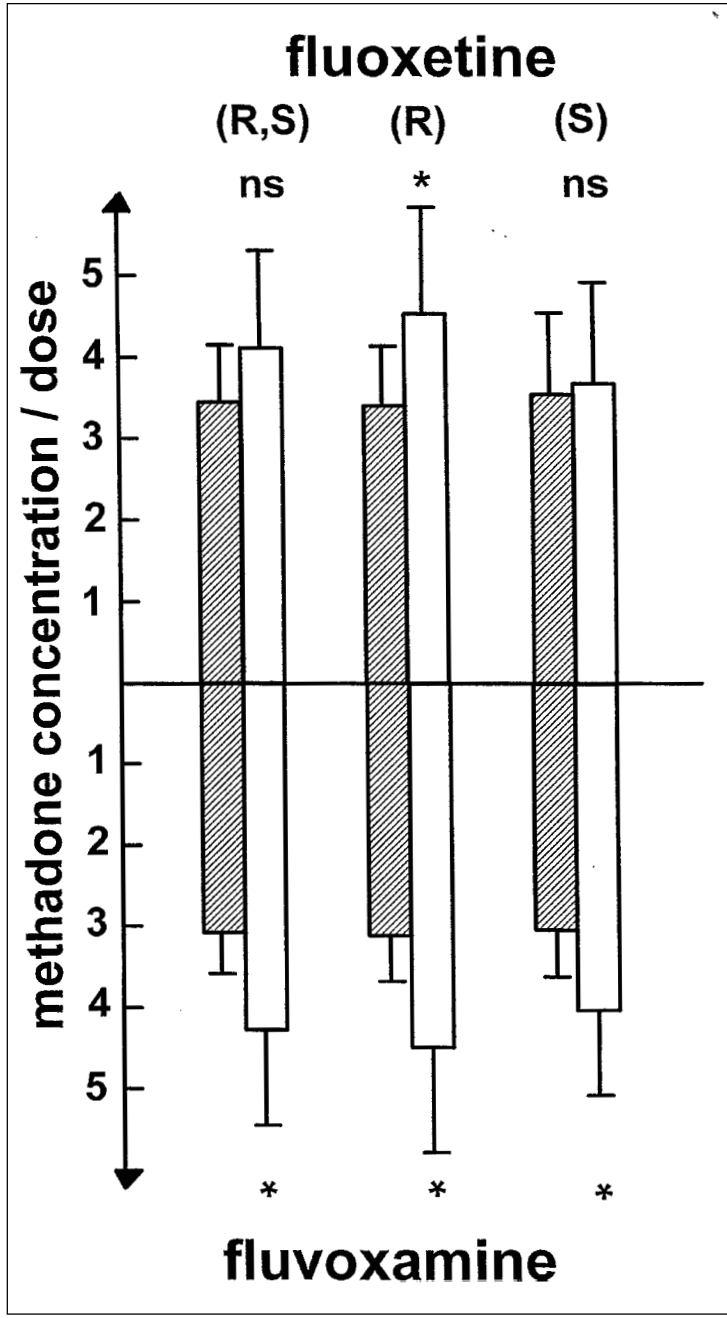

Fig. 2.5. Differential effects of comedication with fluvoxamine and fluoxetine on the plasma concentration of the enantiomers of methadone in methadone-treated patients (after Eap et al 1997)[85] Hatched and white bars: before and after addition of the SSRIs, respectively. *:$P<0.05$.

test (c.f. above), both before and during treatment with sertraline (mean daily dose: 93.5 mg), there was no evidence for inhibition of CYP1A2 activity by this SSRI.[92]

In conclusion, citalopram and sertraline appear to be the SSRIs with the lowest interaction potential. In this respect, their actions contrast with those of fluvoxamine, fluoxetine and paroxetine but these latter drugs differ in their inhibition of cytochrome P450 isozymes, as shown here. Much work has been done to characterize the potential for interactions between SSRIs and cytochrome P450. This knowledge is highly relevant to clinical practice. However, the exact mechanisms by which these drugs are metabolized need to be investigated more closely, especially with regard to which other enzymatic systems might also be implicated.

References

1. Noble S, Benfield P. Citalopram: A review of its pharmacology, clinical efficacy and tolerability in the treatment of depression. CNS Drugs 1997; 8:410-431.
2. Harris MG, Benfield P. Fluoxetine: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in older patients with depressive illness. Drugs and Aging 1995; 6:64-84.
3. Gram LF. Drug Therapy—Fluoxetine. N Engl J Med 1994; 331:1354-1361.
4. Wilde MI, Plosker GL, Benfield P. Fluvoxamine: An updated review of its pharmacology, and therapeutic use in depressive illness. Drugs 1993; 46:895-924.
5. Gunasekara NS, Noble S, Benfield P. Paroxetine: An update of its pharmacology and therapeutic use in depression and a review of its use in other disorders. Drugs 1998; 55:85-120.
6. Murdoch D, McTavish D. Sertraline. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depression and obsessive-compulsive disorder. Drugs 1992; 44:604-624.
7. Anderson IM, Tomenson BM. The efficacy of selective serotonin re-uptake inhibitors in depression: A meta-analysis of studies against tricyclic antidepressants. J Psychopharmacol 1994; 8:238-249.
8. Kasper S, Höflich G, Scholl H-P et al. Safety and antidepressant efficacy of selective serotonin re-uptake inhibitors. Hum Psychopharmacol 1994; 9:1-12.
9. Eap CB, Baumann P. Analytical methods for the quantitative determination of selective serotonin reuptake inhibitors for therapeutic drug monitoring purposes in patients. J Chromatogr B: Biomed Appl 1996; 686:51-63.
10. Baumann P, Rochat B. Comparative pharmacokinetics of selective serotonin reuptake inhibitors: A look behind the mirror. Int Clin Psychopharmacol 1995; 10 (suppl. 1):15-21.
11. Stanford SC. Prozac: Panacea or puzzle? Trends Pharmacol Sci 1996;17:150-154.
12. de Jonghe F, Swinkels J. Selective serotonin reuptake inhibitors—Relevance of differences in their pharmacological and clinical profiles. CNS Drugs 1997; 7:452-467.
13. Brøsen K. Drug-metabolizing enzymes and therapeutic drug monitoring in psychiatry. Ther Drug Monit 1996; 18:393-396.
14. Bertilsson L, Dahl M-L, Sjöqvist F et al. Molecular basis for rational megaprescribing in ultrarapid hydroxylators of debrisoquine. Lancet 1993; 341:63
15. Bertilsson L. Geographical/interracial differences in polymorphic drug oxidation. Clin Pharmacokinet 1995; 29:192-209.
16. Meyer UA. Overview of enzymes of drug metabolism. J Pharmacokinet Biopharm 1996; 24:449-459.
17. Von Moltke LL, Greenblatt DJ, Duan SX et al. Human cytochromes mediating N-demethylation of fluoxetine in vitro. Psychopharmacol 1997; 132:402-407.
18. Shader RI, et al. Personal communication.
19. Schmider J, Greenblatt DJ, Von Moltke LL, et al. Inhibition of CYP2C9 by selective serotonin reuptake inhibitors in vitro: studies of phenytoin p-hydroxylation. Br J Clin Pharmacol 1997; 44:495-498.

20. Dechant KL, Clissold SP. Paroxetine: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depressive illness. Drugs 1991; 41:225-253.
21. Brøsen K. The pharmacogenetics of the selective serotonin reuptake inhibitors. Clin Invest 1993; 71:1002-1009.
22. Preskorn SH. Clinically relevant pharmacology of selective serotonin reuptake inhibitors: An overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism. Clin Pharmacokinet 1997; 32 (suppl. 1):1-21.
23. Baumann P. Pharmacokinetic-pharmacodynamic relationship of the selective serotonin reuptake inhibitors. Clin Pharmacokinet 1996; 31:444-469.
24. Kragh-Sørensen P, Fredricson Overø K, Petersen OL et al. The kinetics of citalopram: Single and multiple dose studies in man. Acta Pharmacol Toxicol 1981; 48:53-60.
25. Baumann P, Larsen F. The pharmacokinetics of citalopram. Rev Contemp Pharmacother 1995; 6:287-295.
26. Priskorn M, Larsen F, Segonzc A et al. Pharmacokinetic interaction study of citalopram and cimetidine in healthy subjects. Eur J Clin Pharmacol 1997; 52:241-242.
27. Lemberger L, Bergstrom RF, Wolen RL et al. Fluoxetine: Clinical pharmacology and physiologic disposition. J Clin Psychiatry 1985; 46:14-19.
28. Aronoff GR, Bergstrom RF, Pottratz ST et al. Fluoxetine kinetics and protein binding in normal and impaired renal function. Clin Pharmacol Ther 1984; 36:138-144.
29. Spigset O, Granberg K, Hägg S et al. Relationship between fluvoxamine pharmacokinetics and CYP2D6/CYP2C19 phenotype polymorphisms. Eur J Clin Pharmacol 1997; 52:129-133.
30. DeVane CL, Gill HS. Clinical pharmacokinetics of fluvoxamine: Applications to dosage regimen design. J Clin Psychiatry 1997; 58 (suppl. 5):7-14.
31. Bayer AJ, Roberts NA, Allen EA et al. The pharmacokinetics of paroxetine in the elderly. Acta Psychiatr Scand 1986; 80(suppl.350):85-86.
32. Kaye CM, Haddock RE, Langley PF et al. A review of the metabolism and pharmacokinetics of paroxetine in man. Acta Psychiatr Scand 1989; 80(suppl.350):60-75.
33. Sindrup SH, Brøsen K, Gram LF et al. The relationship between paroxetine and the sparteine oxidation polymorphism. Clin Pharmacol Ther 1992; 51:278-287.
34. Sindrup SH, Brøsen K, Gram LF. Pharmacokinetics of the selective serotonin reuptake inhibitor paroxetine—nonlinearity and relation to the sparteine oxidation polymorphism. Clin Pharmacol Ther 1992; 51:288-295.
35. Ronfeld RA, Tremaine LM, Wilner KD. Pharmacokinetics of sertraline and its *N*-demethyl metabolite in elderly and young male and female volunteers. Clin Pharmacokinet 1997; 12(suppl.1):23-30.
36. Rochat B, Kosel M, Boss G et al. Stereoselective biotransformation of the selective serotonin reuptake inhibitor, citalopram, and its demethylated metabolites by monoamine oxidases in human liver. Biochem Pharmacol 1998; 56:15-23.
37. Hyttel J, Bøgesø KP, Perregaard J et al. The pharmacological effect of citalopram resides in the (S)-(+)- enantiomer. Short communication. J Neural Transm Gen Sect 1992; 88:157-160.
38. Rochat B, Amey M, Baumann P. Analysis of enantiomers of citalopram and its demethylated metabolites in plasma of depressive patients using chiral reverse-phase liquid chromatography. Ther Drug Monit 1995; 17:273-279.
39. Sidhu J, Priskorn M, Poulsen M et al. Steady-state pharmacokinetics of the enantiomers of citalopram and its metabolites in humans. Chirality 1997; 9:686-692.
40. Sindrup SH, Brøsen K, Hansen MGJ et al. Pharmacokinetics of citalopram in relation to the sparteine and the mephenytoin oxidation polymorphisms. Ther Drug Monit 1993;15:11-17.
41. Rochat B, Amey M, Gillet M et al. Identification of three cytochrome P450 isozymes involved in N-demethylation of citalopram enantiomers in human liver microsomes. Pharmacogenetics 1997; 7:1-10.
42. Bondolfi G, Chautems C, Rochat B et al. Non-response to citalopram in depressive patients: Pharmacokinetic and clinical consequences of a fluvoxamine augmentation. Psychopharmacol 1996; 128:421-425.

43. Foglia JP, Pollock BG, Kirshner MA et al. Plasma levels of citalopram enantiomers and metabolites in elderly patients. Psychopharmacol Bull 1997; 33:109-112.
44. Fjordside L, Jeppesen U, Eap CB et al. The stereoselective metabolism of fluoxetine in poor and extensive metabolisers of sparteine. Eur J Clin Pharmacol 1997; 52(suppl.):A127.
45. Fjordside L, Jeppesen U, Eap CB et al. The stereoselective metabolism of fluoxetine in poor and extensive metabolisers of sparteine. Pharmacogenetics 1999; 9:55-60.
46. Seifritz E, Baumann P, Müller MJ et al. Neuroendocrine effects of a 20-mg citalopram infusion in healthy males—A placebo-controlled evaluation of citalopram as 5-HT function probe. Neuropsychopharmacol 1996; 14:253-263.
47. Altamura AC, Moro AR, Percudani M. Clinical pharmacokinetics of fluoxetine. Clin Pharmacokinet 1994; 26:201-214.
48. Warrington SJ. Clinical implications of the pharmacology of sertraline. Int Clin Psychopharmacol 1991; 6(suppl.2):11-21.
49. Baumann P, Nil R, Bertschy G et al. A double-blind double-dummy study of citalopram comparing infusion versus oral administration. J Affect Disord 1998; 49:195-201.
50. Wong DT, Fuller RW, Robertson DW. Fluoxetine and its two enantiomers as selective serotonin uptake inhibitors. Acta Pharm Nord 1990; 2:171-179.
51. Wong DT, Bymaster FP, Reid LR et al. Norfluoxetine enantiomers as inhibitors of serotonin uptake in rat brain. Neuropsychopharmacology 1993; 8:337-344.
52. Torok-Both GA, Baker GB, Coutts RT et al. Simultaneous determination of fluoxetine and norfluoxetine enantiomers in biological samples by gas chromatography with electron-capture detection. J Chromatogr Biomed Appl 1992; 579:99-106.
53. Hamelin BA, Turgeon J, Vallée F et al. The disposition of fluoxetine but not sertraline is altered in poor metabolizers of debrisoquin. Clin Pharmacol Ther 1996; 60:512-521.
54. Urichuk LJ, Aspeslet LJ, Holt A et al. Determination of p-trifluoromethylphenol, a metabolite of fluoxetine, in tissues and body fluids using an electron-capture gas chromatographic procedure. J Chromatog B 1997; 698:103-109.
55. Marchioni E, Perucca E, Soragna D et al. Choreiform syndrome associated with fluoxetine treatment in a patient with deficient CYP2D6 activity. Neurology 1996; 46:853.
56. Spigset O, Carleborg L, Hedenmalm K, et al. Effect of cigarette smoking on fluvoxamine pharmacokinetics in humans. Clin Pharmacol Ther 1995; 58:399-403.
57. Tulloch IF, Johnson AM. The pharmacologic profile of paroxetine, a new selective serotonin reuptake inhibitor. J Clin Psychiatry 1992; 53 (suppl. 2):7-12.
58. DeVane CL. Pharmacokinetics of the newer antidepressants: Clinical relevance. Am J Med 1994; 97 (suppl.6A):6A-13S-6A-23S.
59. Amsterdam JD, Fawcett J, Quitkin FM et al. Fluoxetine and norfluoxetine plasma concentrations in major depression: A multicenter study. Am J Psychiatry 1997; 154:963-969.
60. Gupta RN, Dziurdzy SA. Therapeutic monitoring of sertraline. Clin Chem 1994; 40:498-499.
61. Baumann P. Care of depression in the elderly: Comparative pharmacokinetics of SSRIs Intl Clin Psychopharmacol 1998; 13(suppl5):S35-S43.
62. Aranow RB, Hudson JI, Pope HG et al. Elevated antidepressant plasma levels after addition of fluoxetine. Am J Psychiatry 1989; 146:911-913.
63. Shimada T, Yamazaki H, Mimura M et al. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. J Pharmacol Exp Ther 1994; 270:414-423.
64. Jeppesen U, Gram LF, Vistisen K et al. Dose-dependent inhibition of CYP1A2, CYP2C19 and CYP2D6 by citalopram, fluoxetine, fluvoxamine and paroxetine. Eur J Clin Pharmacol 1996; 51:73-78.
65. Rasmussen BB, Mäenpää J, Pelkonen O et al. Selective serotonin reuptake inhibitors and theophylline metabolism in human liver microsomes: potent inhibition by fluvoxamine. Br J Clin Pharmacol 1995; 39:151-159.
66. Von Moltke LL, Greenblatt DJ, Duan SX et al. Phenacetin *O*-demethylation by human liver microsomes in vitro: Inhibition by chemical probes, SSRI antidepressants, nefazodone and venlafaxine. Psychopharmacology 1996; 128:398-407.

67. Crewe HK, Lennard MS, Tucker GT et al. The effect of selective serotonin re-uptake inhibitors on cytochrome P4502D6 (CYP2D6) activity in human liver microsomes. Br J Clin Pharmacol 1992; 34:262-265.
68. Richelson E. Pharmacokinetic drug interactions of new antidepressants: A review of the effects on the metabolism of other drugs [review]. Mayo Clin Proc 1997; 72:835-847.
69. Bertz RJ, Granneman GR. Use of in vitro and in vivo data to estimate the likelihood of metabolic pharmacokinetic interactions. Clin Pharmacokinet 1997; 32:210-258.
70. Brøsen K. Are pharmacokinetic drug interactions with the SSRIs an issue? Int Clin Psychopharmacol 1996; 11 (suppl. 1):23-27.
71. Sproule BA, Naranjo CA, Bremner KE et al. Selective serotonin reuptake inhibitors and CNS drug interactions. Clin Pharmacokinet 1997; 33:454-471.
72. Harvey AT, Preskorn SH. Cytochrome P450 enzymes: interpretation of their interactions with selective serotonin reuptake inhibitors. Part II. J Clin Psychopharmacol 1996; 16:345-355.
73. Haselberger MB, Freedman LS, Tolbert S. Elevated serum phenytoin concentrations associated with coadministration of sertraline. J Clin Psychopharmacol 1997; 17:107-109.
74. Rapeport WG, Muirhead DC, Biol C et al. Absence of effect of sertraline on the pharmacokinetics and pharmacodynamics of phenytoin. J Clin Psychiatry 1996; 57 (suppl. 1):24-28.
75. Strauss WL, Layton ME, Dager SR. Brain elimination half-life of fluvoxamine measured by ^{19}F magnetic resonance spectroscopy. Am J Psychiatry 1998; 155:380-384.
76. Gram LF, Hansen MGJ, Sindrup SH et al. Citalopram: Interaction studies with levomepromazine, imipramine, and lithium. Ther Drug Monit 1993; 15:18-24.
77. Baettig D, Bondolfi G, Montaldi S, et al. Tricyclic antidepressant plasma levels after augmentation with citalopram: A case study. Eur J Clin Pharmacol 1993; 44:403-405.
78. Syvälahti EKG, Taiminen T, Saarijärvi S et al. Citalopram causes no significant alterations in plasma neuroleptic levels in schizophrenic patients. J Int Med Res 1997; 25:24-32.
79. Neuvonen PJ, Pohjola-Sintonen S, Tacke U et al. Five fatal cases of serotonin syndrome after moclobemide-citalopram or moclobemide-clomipramine overdoses. Lancet 1993; 342:1419.
80. Laine K, Anttila M, Heinonen E et al. Lack of adverse interactions between concomitantly administered selegiline and citalopram. Clin Neuropharmacol 1997; 20:419-433.
81. Stevens JC, Wrighton SA. Interaction of the enantiomers of fluoxetine and norfluoxetine with human liver cytochromes P450. J Pharmacol Exp Ther 1993; 266:964-971.
82. Conus P, Bondolfi G, Eap CB et al. Pharmacokinetic fluvoxamine—Clomipramine interaction with favorable therapeutic consequences in therapy-resistant depressive patients. Pharmacopsychiatry 1996; 29:108-110.
83. Baumann P, Broly F, Kosel M et al. Ultrarapid metabolism of clomipramine in a therapy-resistant depressive patient, as confirmed by CYP2D6 genotyping. Pharmacopsychiatry 1998; 31:72.
84. Szegedi A, Wiesner J, Hiemke C. Improved efficacy and fewer side effects under clozapine treatment after addition of fluvoxamine. J Clin Psychopharmacol 1995; 15:141-143.
85. Eap CB, Bertschy G, Powell K et al. Fluvoxamine and fluoxetine do not interact in the same way with the metabolism of the enantiomers of methadone. J Clin Psychopharmacol 1997; 17:113-117.
86. Alderman J, Preskorn SH, Greenblatt DJ et al. Desipramine pharmacokinetics when coadministered with paroxetine or sertraline in extensive metabolizers. J Clin Psychopharmacol 1997; 7:284-291.
87. Kurtz DL, Bergstrom RF, Goldberg MJ et al. The effect of sertraline on the pharmacokinetics of desipramine and imipramine. Clin Pharmacol Ther 1997; 62:145-156.
88. Sproule BA, Otton SV, Cheung SW et al. CYP2D6 inhibition in patients treated with sertraline. J Clin Psychopharmacol 1997; 17:102-106.
89. Özdemir V, Naranjo CA, Herrmann N et al. Paroxetine potentiates the central nervous system side effects of perphenazine: Contribution of cytochrome P4502D6 inhibition in vivo. Clin Pharmacol Ther 1997; 62:334-347.

90. Martin DE, Zussman BD, Everitt DE et al. Paroxetine does not affect the cardiac safety and pharmacokinetics of terfenadine in healthy adult men. J Clin Psychopharmacol 1997; 17:451-459.
91. Preskorn SH, Alderman J, Greenblatt DJ et al. Sertraline does not inhibit cytochrome P450 3A-mediated drug metabolism in vivo. Psychopharmacol Bull 1997; 33:659-665.
92. Özdemir V, Naranjo CA, Herrmann N et al. The extent and determinants of changes in CYP2D6 and CYP1A2 activities with therapeutic doses of sertraline. J Clin Psychopharmacol 1998; 18:55-61

CHAPTER 3

SSRIs in Depression: Distinctive Actions?

Julie Newman and Andrew A. Nierenberg

The introduction of the selective serotonin reuptake inhibitors (SSRIs) has radically changed the treatment of depression worldwide. The five currently marketed SSRIs, fluoxetine, sertraline, paroxetine, fluvoxamine and citalopram were accepted by international regulatory agencies because these medications were found to be superior to placebo and, at least for most clinical populations, of equal efficacy when compared to the older generations of tricyclic antidepressants (TCAs). The SSRIs are considered to be equally effective for the treatment of depression and share more similarities than differences. Differences in the onset of action has been a subject of debate among the pharmaceutical houses but most clinicians believe that the timing of clinical effect is the same for each of the SSRIs. Similarly, potential differences in side-effects have been exploited by pharmaceutical advertising and marketing-directed research but, again, most clinicians believe that the side-effect profiles of the SSRIs are more alike than different. To clarify the extent of differences and similarities, this chapter will explore the clinically relevant data amongst the five SSRIs.

Comparison with Other Antidepressants

In terms of tolerability and toxicity, the SSRIs appear to be more acceptable to both patients and their physicians than older antidepressants. Some investigators, however, believe that the TCAs and monoamine oxidase inhibitors (MAOIs) are more effective than the SSRIs in certain subtypes of depression. While the data are mixed, as will be discussed below, most studies indicate that the SSRIs and TCAs are equally efficacious.

Tricyclic Antidepressants (TCAs)

The influential studies from the Danish University Antidepressant Group (DUAG) in 1986[1] and in 1990[2] sparked an ongoing debate on the relative efficacy of SSRIs and tricyclic antidepressants: specifically, that the TCAs are superior for endogenous depression. The DUAG group compared clomipramine to citalopram in one study and to paroxetine in another, in inpatients with major depression. The first study of 114 inpatients found that 62% responded to clomipramine and 34% to citalopram. Similarly, in the second study, 46% responded to clomipramine and only 19% responded to paroxetine after 6 weeks of treatment. Of note, the DUAG generalized clomipramine to all TCAs when clomipramine is anything but a prototypical TCA with regard to its mechanism of action and, among the TCAs, its unique efficacy in obsessive-compulsive disorder (OCD). It might be more accurate to conclude that clomipramine is superior to at least two SSRIs in severely depressed inpatients and not to conclude that these data can be generalized to all TCAs and all SSRIs.[3,4]

Selective Serotonin Reuptake Inhibitors (SSRIs): Past, Present and Future,
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Roose and colleagues[5] compared nortriptyline to fluoxetine in geriatric melancholic depressed inpatients in a hybrid design that blended a head-to-head study (nortriptyline compared to fluoxetine) with data from prior studies of nortriptyline at their center, in a non-randomized assignment. They found that, analyzing all randomized patients (i.e., intent-to-treat analysis), 67% responded to nortriptyline and 23% responded to fluoxetine after 7 weeks of treatment.

Despite these often cited studies, there remains a general consensus that SSRIs are equally effective with TCAs for moderate major depressive disorder.[6] A meta-analysis by Montgomery et al[7] of 42 randomized controlled studies of over 4000 patients found SSRIs to be equivalent in efficacy to imipramine and amitriptyline. No significant differences were found in patients who dropped out due to lack of efficacy, but significantly fewer patients discontinued studies due to side-effects from the SSRIs compared to the TCAs. The higher discontinuation rate with tricyclics, however, may be due to a subtle bias with TCAs being started at high doses rather than using slower and more tolerable dose escalations. Another meta-analysis[8] of randomized clinical trials also indicated equal efficacy between SSRIs and TCAs (44 trials with non-clomipramine TCAs and 7 with clomipramine). A large randomized study of 536 depressed patients in a primary care setting provided further evidence for comparable efficacy between SSRIs and TCAs. No differences were found between fluoxetine and desipramine or imipramine in terms of clinical outcomes, treatment costs, or quality of life.[9]

George and Lydiard[10] reviewed 11 double-blind, placebo-controlled trials specifically looking for differences in onset of action between fluoxetine and TCAs but found no differences. A large study of depressed patients comparing paroxetine, imipramine and placebo did find a difference in onset of action between these two antidepressants. Paroxetine was superior to placebo after one week, but imipramine and placebo were not different until week two.[11]

In summary, head-to-head comparisons between TCAs and SSRIs indicate equal efficacy and onset of action but slightly different side-effects. SSRIs have greater tolerability, less cardiotoxicity, sedation, weight gain, and anticholinergic side-effects.

Atypical Antidepressants

Unlike the wealth of data comparing SSRIs and TCAs, there is a paucity of data comparing most of the atypical antidepressants to the SSRIs, with the exception of trazodone.

The literature suggests that the SSRIs and trazodone are equally effective in treating major depression. A meta-analysis by Workman and Short[12] found no difference in effect size between imipramine, trazodone, bupropion and fluoxetine. A review by Haria et al[13] suggests that trazodone at therapeutic doses in elderly depressed patients was as effective as TCAs and fluoxetine. Yet there are only five studies which directly compare trazodone to fluoxetine and no studies with the other SSRIs. A small double-blind study of geriatric depressed patients found a non-significant trend favoring fluoxetine over trazodone in efficacy in the 13 completers, only three of whom were on trazodone.[14] A larger double-blind study (N = 126) found equal efficacy between fluoxetine (median dose: 20 mg/day) and trazodone (median dose: 250 mg/day) but with more patients reporting activating effects with fluoxetine and more reporting sedating side-effects with trazodone.[15] In a double-blind trial with 40 depressed outpatients, trazodone (50-400 mg/day) had a more rapid response than fluoxetine (20-60 mg/day) by week 3 on both the Hamilton rating scale for depression (HAM-D) and the Clinical Global Impressions (CGI) scale but no difference at 6 weeks.[16] Yet, it is possible that the fluoxetine group had a slower onset of action because they were more chronically ill. In the fluoxetine group, 67% of patients had greater than one year duration of their current depressive episode, compared to 35% in the trazodone group. Another double-blind study found the reverse: i.e., fluoxetine had a superior clinical response

at weeks 1 and 2, compared to trazodone[17] although, at week 6, there was no significant difference between the groups. Trazodone, however, did demonstrate improvement on sleep disturbance scores.

Despite studies finding equal efficacy between trazodone and fluoxetine, trazodone has had limited success in the market as an antidepressant, in part because therapeutic doses often cause intolerable sedation. An example of this was an open-label study of fluoxetine and trazodone in 18 patients with double depression (major depression superimposed on dysthymia). The dropout rate with fluoxetine was 7.7%, but 80% with trazodone.[18]

Only two studies have compared nefazodone with a SSRI in major depression. One double-blind study compared nefazodone (100-600 mg/day) to sertraline (50-200 mg/day) in 160 patients with major depression.[19] The two medications had equal efficacy but only sertraline had negative effects on sexual function. In another study with 206 outpatients, paroxetine (mean dose: 32.7 mg/day) and nefazodone (mean dose: 472 mg/day) were found to be equally effective and well tolerated.[20]

In Preskorn's review[21] of comparative tolerability of the newer antidepressants, he reported that nefazodone had fewer cumulative treatment-emergent adverse effects than fluoxetine. While most side-effects were less frequently reported, nefazodone was associated with more dizziness, confusion and vision disturbance than the SSRIs. One problem with this review was that side-effects were compared using placebo-adjusted rates. Preskorn simply subtracted the rates of side-effects with placebo from the rates with the active drugs. Relative risk ratios (RRs) may be a better measure to compare side-effects occurrences.

Venlafaxine has been compared head-to-head with fluoxetine in two studies. Dierick et al[22] compared venlafaxine and fluoxetine in a double-blind trial with 314 outpatients. The initial dose was 75 mg/day for venlafaxine and 20 mg/day for fluoxetine. If the patient had an inadequate result after two weeks, venlafaxine was increased to 150 mg/day but fluoxetine remained at 20 mg/day. Using HAM-D, fluoxetine at 20 mg/day was found to be equally effective with 75 mg of venlafaxine, but inferior to 150 mg of venlafaxine, although no difference overall was found on the CGI. In another study comparing the two medications in 68 melancholic depressed inpatients, venlafaxine (200 mg/day) was found to be superior to fluoxetine (40 mg/day). At 4 weeks, venlafaxine had significantly more responders than fluoxetine (76% and 41%, respectively) but the difference, while still favoring venlafaxine, was not significant at week 6. Both medications had similar tolerability.[23] Preskorn,[21] however, found that compared with fluoxetine, paroxetine and sertraline, venlafaxine had the highest incidence of nausea and anorexia when using placebo-adjusted incidence rates from Physician's Desk Reference (1997) (PDR) databases.

There is little data about bupropion compared with the SSRIs with no published head-to-head trials. Preskorn[21] reported that bupropion had a higher rate of tremors than fluoxetine, sertraline or paroxetine but, again, using placebo-adjusted rates. There are also no published studies directly comparing mirtazapine and any SSRI. Mirtazapine has been shown to be more effective than placebo and equally effective to amitriptyline. There was no significant difference with amitriptyline and mirtazapine in a meta-analysis that included five studies with 732 patients.[24] Mirtazapine has also been shown to be equally effective to other antidepressants in nine comparative studies of mirtazapine.[25]

Monoamine Oxidase Inhibitors (MAOIs)

Although MAOIs have been used effectively for years, only three studies have compared them directly with the SSRIs, all with fluoxetine. Pande et al[26] compared fluoxetine (20-60 mg/day) and phenelzine (45-90 mg/day) in a double-blind study of atypical depressed patients. The 38 completers had equal response to the two medications but with more adverse effects from phenelzine. Williams et al[27] found equal efficacy in a

double-blind study with fluoxetine (20-40 mg/day) and the reversible MAOI, moclobemide, (300-600 mg/day) in 122 patients with major depression. Fluoxetine-treated patients reported more sedation, nausea and vomiting, while moclobemide patients complained more of insomnia, although the differences in these side-effects were not statistically significant. A larger study compared moclobemide (300-450 mg/day) and fluoxetine (20-40 mg/day) in a double-blind trial with 209 atypically depressed patients; 67% patients had a response (50% reduction in HAM-D) with moclobemide and 57% with fluoxetine, a non-significant difference. There was a statistically significant difference in Montgomery-Asberg depression rating scale (MADRS) and CGI ratings, however, favoring moclobemide as some of the fluoxetine group actually worsened.[28]

Within-Group Comparison of SSRIs

Efficacy

General clinical impressions of the existing five SSRI antidepressants suggest that all are equally effective. This equal effectiveness is confirmed in 15 of 18 SSRI head-to-head published studies. Geretsegger et al[29] found that paroxetine (20-40 mg/day) was superior to fluoxetine (20-60 mg/day) in 106 geriatric in- and outpatients. More patients treated with paroxetine were responders, and improvements in both depression scales and cognitive scales were seen by week 3. Of the other two studies that did show differences in efficacy, one indicated that, in intent-to-treat analysis, sertraline was better than paroxetine but there was no difference in completer analysis. Of note, this study had a 41% (9/22) dropout rate in the paroxetine group due to side-effects, most likely due to a rapid titration up to 50 mg.[30] In the other study, paroxetine was superior to fluoxetine in geriatric outpatients but the proportion of responders was low for both drugs (38% and 17%, respectively).[31] One study using sertraline and fluoxetine in geriatric patients found a significant difference in cognitive function between the two groups, but not in antidepressant response.[32] The sertraline group had better scores in two tests: Digit Symbol and Shopping List. Unfortunately, little other information was given as this study was published only in abstract form. It is worth noting that of the other studies that did not find efficacy differences between two SSRIs, most of them were not large enough to detect small differences in efficacy if they did in fact exist (Table 3.1).

As with the findings of equal efficacy, 11 of 18 published head-to-head studies of two SSRIs indicate similar time to onset of action. It is generally agreed that the onset of action of antidepressants is between two and four weeks without a significant difference between the medications. Several published studies, however, did indicate that citalopram and paroxetine, two SSRIs with shorter half-lives, have a faster onset of action than fluoxetine.[29,31,34,38,39] Three studies found that paroxetine was superior to fluoxetine by week three.[29,31,34] Ontiveros and Garcia-Barriga[39] found that paroxetine showed greater response than fluoxetine by day 14 but not after six weeks. In contrast, two studies found differences in onset of action that cannot be explained by differences in half-life. Newhouse[32] found that patients had a better response to sertraline by the second week compared to fluoxetine. Similarly, Nemeroff et al[41] reported that patients responded to sertraline faster than fluvoxamine, a difference that was significant after one week. Overall, time to response for all the SSRIs appears to be equal with the one exception that fluoxetine may take slightly longer to demonstrate its effect.

Table 3.1. Randomized, double-blind trials comparing SSRIs in patients with major depression

Medication and Dose (mg)[1]	Weeks	Sample size and Population	Response rates	Ref. #
Sertraline 50-150 Fluoxetine 20-60	8	108 outpatients	equal efficacy	33
Paroxetine 20-40 Fluoxetine 20-60	6	78 outpatients	paroxetine significantly reduced anxiety and had more responders at 3 weeks; equal efficacy at 6 weeks	34
Paroxetine 20-40 Fluoxetine 20-60	6	90 outpatients	equal efficacy; significantly more weight loss with fluoxetine	35
Paroxetine 20-40 Fluoxetine 20-60	6	106 geriatric outpatients	paroxetine significantly decreased cognitive scale at week 3 and decreased HAM-D rating at weeks 3 and 6	31
Paroxetine 20 Fluoxetine 20	6	178 inpatients	equal efficacy	36
Paroxetine 20-30 Fluvoxamine 50-200	6	120 in- or outpatients	equal efficacy; significantly more somnolence with paroxetine	37
Paroxetine 20-40 Fluoxetine 20-60	6	106 in- or outpatients	paroxetine superior at weeks 3 and 6 for HAM-D and cognitive rating; more dizziness with paroxetine; more constipation with fluoxetine	29[3]

Table 3.1., cont. Randomized, double-blind trials comparing SSRIs in patients with major depression

Medication and Dose (mg)[1]	Weeks	Sample size and Population	Response rates	Ref. #
Fluoxetine 20-40 Sertraline 50-100	12	elderly (number not specified)	equal efficacy but earlier response and better cognitive function with sertraline	32
Fluoxetine 20-40 Sertraline 50-100	12	elderly (number not specified)	equal efficacy but earlier response and better cognitive function with sertraline	32
Paroxetine 20 Fluoxetine 20	6	60 outpatients	equal efficacy; significantly earlier response with paroxetine	39
Sertraline 50-100 Fluoxetine 20-40	6	286 outpatients	equal efficacy	40
Fluvoxamine 50-150 Sertraline 50-200	7	95 outpatients	equal efficacy; setraline response by week 1; less sexual dysfunction with fluvoxamine	41
Sertraline 50-100 Fluoxetine 20-40	32	165 in- and outpatients	equal efficacy; more activating side-effects with fluoxetine	42
Citalopram 30-40 Fluvoxamine 150-200	6	217 outpatients	equal efficacy; less gastrointestinal disturbance with citalopram	43
Fluvoxamine 100-150 Fluoxetine 20-80	7	100 outpatients	equal efficacy; less nausea with fluoxetine	44

Table 3.1., cont. Randomized, double-blind trials comparing SSRIs in patients with major depression

Medication and Dose (mg)[1]	Weeks	Sample size and Population	Response rates	Ref. #
Sertraline 150[2] Paroxetine 50	6	46 inpatients with psychotic symptoms	sertraline superior for patients with intent-to-treat but not for completers	30
Sertraline 100 Fluvoxamine 200	104	64 outpatients in remission	equal efficacy in preventing recurrences	45
Fluvoxamine 50-150 Paroxetine 20-50	7	60 outpatients	equal efficacy; significantly more sweating with paroxetine	46

[1]; single number represents fixed dose or average (otherwise dose range is given)
[2]; titrated doses over 8 days
[3]; unpublished study cited in ref. 28

Side-Effects

General

Compared to older antidepressants, the SSRIs have relatively few side-effects, with the most common ones being gastrointestinal (nausea or vomiting), sedation or agitation, and sexual dysfunction. The reported rates vary widely but often are significantly affected by starting dosages. When side-effects are compared between the SSRIs, 13 of the 18 published head-to-head studies found either no differences or side-effect differences were not reported explicitly.

The majority of the head-to-head studies found no significant differences in adverse side-effects overall, but there were a few exceptions. One study had no overall difference in numbers of side-effects between the medications but found that patients on fluoxetine reported more severe adverse events than those on sertraline.[33] Another study, while also finding no overall differences between the two medications, stated that patients reported less severe side-effects from paroxetine compared to fluvoxamine, the latter group having significantly more dropouts due to adverse side-effects.[37] Zanardi et al[30] also found a difference in dropout rates due to side-effects: there were no dropouts in the sertraline group, but 41% (9/22) dropped out of the paroxetine group, probably due to their titrating all patients to 50 mg of paroxetine by day 8.

Many studies, however, did find some specific side-effects that were significantly different between two SSRIs. Differences in gastrointestinal side-effects including weight loss were found in five studies. A large study found that fluvoxamine (150-200 mg/day) caused significantly more treatment emergent nausea and diarrhea and a trend for more vomiting than citalopram (30-40 mg/day).[43] While another study found that fluvoxamine caused less nausea than fluoxetine,[44] Geretsegger et al[29] found that geriatric patients reported more dizziness and constipation with paroxetine compared to fluoxetine and Tignol[36] found that, compared to paroxetine, fluoxetine had significantly more metabolic/nutritional adverse events due to weight loss: 12.6% for fluoxetine compared to 3.4 % for paroxetine. Gagiano[35] also found that fluoxetine led to significantly more weight loss than paroxetine.

Differences in side-effects related to sedation or agitation/anxiety were reported in four studies. Van Moffaert et al[42] found that fluoxetine caused significantly more activating side-effects (agitation, anxiety and insomnia) than sertraline. Aguglia et al[33] also compared sertraline and fluoxetine and found a higher incidence of agitation, anxiety and insomnia in fluoxetine and a higher incidence of irritability, headache and somnolence with sertraline but they did not specify if this was a significant finding. Bennie et al[40] found a non-significant trend for sertraline to decrease anxiety more than fluoxetine in depressed outpatients. Ansseau et al[37] found significantly more somnolence from paroxetine compared to fluvoxamine, although they considered that this might be in part due to their dosing schedule where paroxetine was given in the morning while fluvoxamine was given in the evening.

Statistical differences between SSRIs for less common side-effects were found in two studies. De Wilde et al[34] found more patients on fluoxetine than paroxetine had adverse events related to the respiratory system and involving skin and appendages. One study suggests that paroxetine causes more sweating compared to fluvoxamine (33% and 10%, respectively).[46] This difference is confirmed indirectly by using data published in the package inserts to compare odds ratios of side-effects (i.e., the ratio of the odds of having a side-effect with active drug and the odds of having a side-effect with placebo) caused by active drug compared to placebo.

Paroxetine, while having a high affinity for 5-HT uptake sites also has low affinity for muscarinic receptors. While clinical lore states that paroxetine has more anticholinergic side-effects than the other SSRIs, this has not been demonstrated clinically. DeWilde et al[34]

found that only 2% of patients had anticholinergic side-effects with paroxetine compared to 6% for fluoxetine.

Preskorn[21] compared data from the 1995 PDR with placebo-adjusted incidence rates of frequent adverse effects with fluoxetine, sertraline and paroxetine. He found that paroxetine had the highest incidence of fatigue, micturation and flatulence. Sertraline had the highest incidence of diarrhea and dyspepsia. However, these results reflect placebo-adjusted rates (the rates of side-effects with placebo subtracted from the rates with the active drugs) and not relative risk ratios.

We compared side-effects rates of the five SSRIs using data from the PDR 1997 and package inserts. Compared to placebo, relative risk ratios (RR) of side-effects were tabulated. For nausea, one of the most common side-effects from SSRIs, citalopram had the lowest RR. Fluoxetine has the highest RR for anorexia, and sweating is most likely to occur with paroxetine treatment. Some side-effects, such as fatigue and agitation, are not reported for all the SSRIs and are categorized under similar but not duplicate names; it is hard to compare them, therefore.

While mild side-effects are common, difficulty tolerating one SSRI does not necessarily mean that another SSRI will cause similar problems. In a study by Brown and Harrison,[47] 85 of 93 patients who were unable to tolerate fluoxetine could tolerate sertraline and 69 of them had a beneficial response. In addition to the common side-effects, there are a few complications that are less common clinically but often cited in the literature. These include hyponatremia and movement disorders.

Hyponatremia caused by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has been associated with fluvoxamine, sertraline, paroxetine and fluoxetine. Liu et al[48] reported on published cases from the Medline database (30 cases) and unpublished data from the pharmaceutical industry, Ontario Medical Association, Health Protection Branch of Health Canada, the US Food and Drug Administration, and the World Health Organization. They found that of 736 reported cases, the majority were associated with fluoxetine (75.3%) but cases were also found with paroxetine (12.4%), sertraline (11.7%) and fluvoxamine. This disproportionate ratio most likely reflects prescribing patterns. Most cases were in patients over 65 years old and the median time to onset was 13 days with a range of 3-120 days.

Movement disorders occurring after initiation of SSRIs are not uncommonly seen in clinical practice and are reported in the literature. In a review of product literature provided by Eli Lilly and Co., Leo[49] reported 375 cases of akathisia, 218 of dystonia, and 76 cases of tardive dyskinesia (TD) associated with fluoxetine as of December 31, 1995. Leo[49] also found 71 case reports of movement disorders in the literature, mostly related to fluoxetine (75%), the most commonly prescribed SSRI at the time. Most reports concerned akathisia (45%), followed by dystonia (28%), parkinsonism (14%), tardive dyskinesia-like movements (11%), and tremors (10%). The majority of cases occurred in women and when patients were on concurrent medications. It appears that movement disorders can occur with all of the SSRIs as cases have been reported with fluoxetine, paroxetine and sertraline. Akathisia is reported commonly in younger patients: a review of case reports found that the average age was 38 years. TD, parkinsonian symptoms and dystonia all were reported more often in older patients with the average age being over 50. Symptoms lasted from hours to months, except for TD which did not always remit after discontinuation of the medications. Mechanisms underlying these effects remain unclear as SSRIs can induce extrapyramidal side-effects in some patients but improve parkinsonism and dystonia in others.

Sexual Dysfunction

Among the more frequent side-effects of the SSRIs, patients complain of sexual dysfunction, especially after they respond and continue to take the medication for a long time.[50] While depression itself lowers libido in many patients, there are infrequent complaints of inhibited arousal or ejaculatory disturbance during early antidepressant treatment. As depression remits, however, persistent sexual dysfunction becomes more problematic to patients.

All the SSRIs have been associated with sexual dysfunction and difficulties have been found during all sexual phases, including lowered libido, erectile and engorgement failure, and anorgasmia. Reported rates of sexual dysfunction have varied greatly and the wide disparity may be explained, in part, by different methods of ascertainment. Rates appear to be lower when spontaneous unstructured inquiry is used in contrast to specific questionnaires. Another possible reason for the discrepancy in rates of dysfunction could be variable dosing of the SSRIs. The incidence of these symptoms for SSRIs and other antidepressants, and the mechanisms underlying them, are discussed in detail in Chapter 6.

Direct comparisons between the SSRIs specifically looking at sexual dysfunction are few. Modell et al[51] gave an anonymous questionnaire to 107 outpatients on antidepressants. 73% of patients on fluoxetine, paroxetine or sertraline reported a decrease in libido, arousal, duration or intensity of orgasm below their premorbid levels, but there was no difference between these three SSRIs. In a head-to-head study with sertraline and fluvoxamine, which specifically looked at sexual function, 28% of sertraline (mean dose: 137 mg/day) patients developed dysfunction compared to only 10% of patients on fluvoxamine (mean dose: 124 mg/day).[41] Prerelease data reveals slightly different rates for the SSRIs but it is likely that different criteria were used and thus the rates cannot be directly compared. Often the focus was on abnormal ejaculation which may explain why some rates have ranged from 1-2% in women to 21% in men.

At this point, there is no clear evidence that one SSRI is superior to another for causing less sexual dysfunction and most clinicians have found few differences between them.

Pharmacokinetics

Although the SSRIs are remarkably similar in efficacy, side-effect profile, and mechanism of action, pharmacokinetic variability exists. Reasons for this are discussed in detail in Chapter 2.

Briefly, SSRIs are well absorbed from oral administration and food co-administration is probably not clinically important.[6,52] While co-administration of food does not lead to plasma alterations of paroxetine, fluvoxamine, and citalopram,[53] it does appear to delay peak plasma levels of fluoxetine by several hours and may also lead to increased absorption of sertraline, although this is still a debatable finding.[54]

The five SSRIs all have large volumes of distribution. There is wide inter-individual variability in steady-state drug concentrations with any given dose of the SSRIs. Yet, unlike the TCAs, where broad variability of levels has clinical implications for efficacy and toxicity, the safer profile of SSRIs and the lack of therapeutic correlation with plasma levels make this variability less important.

While sertraline and citalopram have linear pharmocokinetics, fluoxetine is nonlinear so higher doses lead to a disproportionately higher plasma concentration. Paroxetine has linear kinetics at high levels but nonlinear at lower levels.[52,55]

Protein binding varies among the five SSRIs. Paroxetine, sertraline and fluoxetine are all >95% protein bound but fluvoxamine and citalopram are only about 80% protein bound.[53,54] While drug-drug interactions from displacement of SSRIs bound to plasma

proteins are less likely with citalopram and fluvoxamine, it is probably not particularly clinically relevant for any of the SSRIs.[54]

The SSRIs all are metabolized by the hepatic cytochrome P450 system (CYP450). The metabolism of each of the SSRIs is discussed in Chapter 2. Half-lives of the parent compounds and their active metabolites vary widely; paroxetine has the shortest half-life, averaging 10-20 hours, while fluoxetine and its active metabolites have a half-life of 7-14 days. A short half-life is advantageous if a patient has an adverse reaction to a medication or wants to take a weekend drug holiday for sexual dysfunction. Short half-life medications also require briefer washout periods before switching to a MAOI. A medication with a longer half-life may be preferable for a patient who occasionally misses doses or to avoid possible withdrawal syndromes.

The pharmacokinetics of the SSRIs vary in elderly patients and those with hepatic or renal dysfunction. In elderly patients, minimal effects on elimination half-life are found with fluoxetine and fluvoxamine.[54] Sertraline has a longer half-life in the elderly but not significantly so.[54] The change in clearance for paroxetine and citalopram, however, does warrant lower dosages in the elderly.[53,54]

In hepatic dysfunction, the half-life is increased for fluvoxamine, fluoxetine, citalopram and paroxetine so dosages should be significantly lowered.[6,53,54] Renal dysfunction causes an increase in the half-life of citalopram but does not appear to cause a clinically significant effect.[53] There is little change in fluoxetine and fluvoxamine but there is an increase in paroxetine's peak plasma concentration in patients with poor creatinine clearance.[54] There is limited data about sertraline in this population.

Withdrawal or Discontinuation Syndromes

Since the first case reports of SSRI discontinuation syndromes in 1993, increasing attention has been focused on this phenomenon. Many case reports have described withdrawal reactions following rapid discontinuation of SSRIs and some have been reported when medications were discontinued in double-blind studies[56] (see Chapter 5 for a full discussion of this topic). While there are published reports about all the SSRIs (except citalopram to the best of our knowledge), fewer cases have been reported for fluoxetine, likely due to its longer half-life and active metabolites. There have been no published reports of prospective studies specifically looking at withdrawal reactions.

Criteria for Selection of Preferred Treatment

Matching SSRI to Depressive Subtype

Melancholic or Endogenous Depression

Depression with melancholic features is classified as a loss of pleasure in all or almost all activities, or lack of reactivity to usually pleasurable stimuli, and three of the following: distinct quality of depressed mood, depression worse in the morning, early morning awakening, marked psychomotor retardation or agitation, significant anorexia or weight loss, and excessive or inappropriate guilt.

Traditionally, endogenous depression has responded poorly to placebo.[57] It has also been suggested that SSRIs are relatively ineffective for melancholia and TCAs are often thought to be superior in this population. The DUAG studies[1,2] have been often cited in this regard, as they found that the number of responders to clomipramine was twice that of citalopram (1986) and paroxetine (1990) in endogenously depressed outpatients. Another often cited study, but with significant methodological flaws, looked at older inpatients with depression, some with melancholic features.[5] Patients treated with fluoxetine were

non-randomly compared to "comparable" patients treated with nortriptyline. In melancholic patients who completed the study, nortriptyline had a 67% response rate while only 23% responded to fluoxetine.

Other studies, however, have found SSRIs to be at least equivalent to TCAs in endogenous depression. In a double-blind study of 38 patients with endogenous depression, Gravem et al[58] found citalopram (30-60 mg/day) to be equally effective with amitriptyline (75-225 mg/day). Ginestet[59] found fluoxetine (mean dose: 58 mg/day) as effective as clomipramine (mean dose: 148 mg/day) in 50 inpatients with melancholic depression. Nielsen et al[60] in a 12-week double-blind trial with 36 patients with major depressive disorder (MDD) found that patients on paroxetine (30 mg/day) had significantly lower scores on the melancholia scale after one week than did patients treated with imipramine (150 mg/day). Overall, the two medications had equal efficacy but they did not report separate results for patients with melancholic and non-melancholic depression. They also had high dropout rates (44% for paroxetine and 60% for imipramine). A fourth study found fluovoxamine (150-300 mg/day) superior to imipramine (150-300 mg/day) in a 6-week double-blind trial of 59 inpatients with melancholia.[61] However, as most of these patients had received previous antidepressant treatment, this study may have had a selection bias of patients who had previously failed tricyclic antidepressants.

There are no head-to-head trials between the SSRIs specifically in this population, but some studies have looked at the HAM-D subscale of melancholia. Haffmans et al[43] did not find a difference between fluvoxamine and citalopram in the HAM-D melancholia subscale.

Atypical Depression

Atypical depression is characterized by mood reactivity and two of the following: weight or appetite increase, hypersomnia, leaden paralysis and a pattern of interpersonal rejection sensitivity.[62] MAOIs have been found to be superior to TCAs for atypical depression but recent views are that SSRIs are also an effective treatment for this subtype. Response rates have varied, Nierenberg et al[63] reported that 42% of atypical depressed patients (74/167) responded to a 12-week open trial of fluoxetine. Pande et al[26] found fluoxetine (20-60 mg/day) to have a 80% response rate after 6 weeks for atypical depression, which was equally effective to phenelzine (45-90 mg/day) in their double-blind trial of 42 patients.

Hostile Depression

Hostile depression is a subtype that has received little attention and there have been no comparison trials between the SSRIs in this area. Fava et al[64] found that 44% of 127 outpatients with MDD reported baseline anger attacks. In an open 8-week trial with fluoxetine, 71% of patients reported a disappearance of these anger attacks. In a later double-blind study, this same group compared sertraline and imipramine for anger attacks and found the two medications equally effective.[65]

There is a suggestion that citalopram may be helpful in this subtype but it has not been directly studied. Syvalahti et al[66] found that citalopam (20-60 mg/day) led to a 52% decrease in the hostile-suspicious factor of the Brief Psychiatric rating scale. However, this was an open-label trial in 36 psychotic and borderline patients who were also on neuroleptics.

Anxious and Psychomotor Agitated Depression

As many as 15-33% of depressed patients have panic attacks during their depressed episode and up to 33% of patients with depression have some symptoms of anxiety such as agitation, gastrointestinal symptoms, hypochondriasis, depersonalization, or obsessive-compulsive features.[67] In a naturalistic study of 327 in- and outpatients with primary unipolar depression, Clayton et al[67] found that patients with higher ratings of anxiety had longer

episodes of depression and had a poorer response to treatment with either TCA or MAOIs. Flint and Rifat[68] also found that geriatric patients with major depression and high scores on the subscale of the Hospital Anxiety and Depression scale had significantly poorer response rates to nortriptyline than patients with low anxiety scores.

Although TCAs have been less effective with patients with high anxiety scores, traditionally, clinicians have believed that TCAs, which tend to cause sedation, are more effective than SSRIs for agitated patients. Two studies support this view. Burns et al[69] in a double-blind study compared the TCA, lofepramine, and fluoxetine in 183 in- and outpatients. While both antidepressants had equal response rates, anxiety was a positive predictor of response to lofepramine and a negative predictor of response to fluoxetine. Sheehan et al[70] analyzed a database of depressed patients (95% unipolar): 2963 patients were treated with paroxetine, 554 patients on placebo, and 1151 were treated with TCAs. At week 1, TCAs were superior to paroxetine for reducing somatic anxiety, although the groups were equal by week 6. There was no difference in emergent anxiety in paroxetine or the TCA-treated patients.

Other studies, however, have found no difference between SSRIs and TCAs for anxious depression. In an 8-week double-blind trial with 124 patients with agitated depression, fluoxetine (20-60 mg/day) was equally effective as imipramine (150-300 mg/day), but 29/62 (47%) patients treated with imipramine discontinued due to rapid dose escalation.[71] Ravindran et al[72] found that paroxetine and clomipramine were equally effective in decreasing anxiety and depression in a 12-week double-blind trial of 1019 patients. A meta-analysis of 19 double-blind randomized trials of fluoxetine and placebo or TCAs or both, found that TCAs and fluoxetine were equally effective on both measures of depression and measures of anxiety.[73] A study by Dunbar[74] used a large pooled-data analysis to assess paroxetine versus TCAs in anxious depressed patients. Pooled results found paroxetine superior to the TCAs in HAM-D psychic anxiety scores from week 2 through week 6. Somatic anxiety scores, which included gastrointestinal symptoms, were lower in the first week for the TCAs, but then equal for the TCAs and paroxetine, both of which were superior to placebo. There was no difference in emergent anxiety between the TCAs and paroxetine.

There are no head-to-head studies between the SSRIs specifically looking at anxious depression. However, several studies of depressed patients do include anxiety scores. Agulia et al[33] compared sertraline and fluoxetine in a double-blind study and found no difference between the two groups in improvement of anxiety scores on both the Hamilton anxiety (HAM-A) scale and Zung anxiety scale as well as the somatic anxiety item of the HAM-D scale. When comparing the anxiety/somatization sub-scales of the HAM-D, Patris et al[43] found no difference between citalopram and fluoxetine. Haffmans et al[42] also did not find a statistically significant difference in this sub-scale between citalopram and fluvoxamine. Bennie et al,[40] in a double-blind comparison between sertraline and fluoxetine in 286 outpatients, found only a non-significant trend of sertraline to improve anxiety symptoms on the HAM-A scale.

Overall, despite a small but real risk of SSRI-induced anxiety, data suggest that the SSRIs are equal to the TCAs in reducing anxiety associated with depression and the SSRIs are equal to each other in this regard.

Bipolar Depression

Bipolar depression can be difficult to treat as antidepressants have been known to both induce mania and to decrease cycling length. Fortunately, it appears that manic episodes induced by antidepressants may be more benign. In a retrospective chart review of 98 hospitalized patients, Stoll et al[75] found that antidepressant-induced mania was found to be milder and more time-limited than spontaneous mania.

There is some evidence that the different classes of antidepressants induce mania at different rates. SSRIs might cause less switching to mania than older TCAs. Comparing data from clinical trials from the pharmaceutical companies, Peet[76] reports that bipolar depressed patients switch to mania significantly less often when treated with SSRIs compared to TCAs. Using TCAs in 2716 patients led to a 11.2% switch-rate. In 10,246 patients on SSRIs, only 3.7% switched to mania, the same percentage as placebo. Some evidence suggests that bupropion may be the best choice for bipolar depression. In the study by Stoll et al,[75] patients on MAOIs and bupropion had slightly less severe manic episodes than patients on TCAs or fluoxetine. In a double-blind study of bipolar depression, 5 of 10 patients on desipramine but only 1 of 9 patients on bupropion developed mania or hypomania. All patients were on concurrent mood stabilizers.[77]

Despite the inherent risks in treating bipolar patients with antidepressants, SSRIs can be beneficial for treatment of their depressions. Simpson and DePaulo[78] reported on 16 patients with bipolar II disorder who had a poor response to TCAs. Fluoxetine (dose range: 20-60 mg/day) resulted in partial or full response in 15/16 patients with 3 developing mild hypomanic or mild mixed symptoms. A double-blind study by Cohn et al[79] found that bipolar depressed patients had a 86% response rate with fluoxetine, significantly more than the 57% response rate with imipramine, although there was a high dropout rate in the latter group. Most of these patients were maintained on lithium, so there were only a small number of switches to mania.

Induction of mania or hypomania in patients previously thought to have unipolar depression is less common. In premarketing trials, sertraline was associated with a 0.4% induction of mania or hypomania and paroxetine with a 1% switch. Peet[76] reports that switching induced by antidepressants in this population is not significantly different from placebo.

Psychotic Depression

Major depression with psychotic features has been traditionally treated with TCAs and antipsychotics. It appears that the combination of SSRIs and antipsychotics may be equally effective. Rothschild et al[80] published the first report of SSRIs being used to treat psychotic depression. Fluoxetine plus perphenazine led to a 73% (22/30) response rate in psychotic depressed patients, comparable to response rates of TCAs and antipsychotics.

It has recently been proposed that SSRIs alone may be an effective treatment for this subtype. In a small double-blind study, Zanardi et al[30] found a 75% response rate for sertraline and a 46% response for paroxetine (not statistically different) for inpatients with psychotic depression without concomitant antipsychotics. Gatti et al[81] found that 48 of 57 inpatients with delusional depression responded to treatment only with fluvoxamine (300 mg/day): a response comparable to the combination of antidepressants and antipsychotics. Syvalahti et al[66] used citalopam (20-60 mg/day) in 36 psychotic and borderline patients who had had an unsatisfactory response to neuroleptics. Sixty-five percent (22/36) of patients had clinically significant improvement when citalopram was added. This study, however, was limited due to the lack of specification about the patients' diagnoses.

Retarded Depression

There is little data to support the use of one SSRI in preference to another in major depression with psychomotor retardation. In one head-to-head study of fluoxetine and sertraline, no difference was found in improvement of retardation on the HAM-D scale.[33] This was also found for citalopram and fluvoxamine in a study by Haffmans et al.[43] Unpublished data from Eli Lilly and Co. suggest that fluoxetine may be superior for retarded depression compared to agitated depression in the first 2-3 weeks, but no differences are

apparent after that. This result, however, has not been confirmed by a smaller study.[82] It seems that this discrepancy is more likely to be related to agitation side-effects frequently seen with the SSRIs rather than an inherent advantage for a subtype of depression.

Matching SSRI to Comorbidity

Obsessive-Compulsive Disorder (OCD)

In patients with OCD, there is a high comorbidity with depression and lifetime prevalence of depression has been estimated as high as 80%. All the SSRIs have been shown to be more effective than placebo in OCD, but there are few studies specifically addressing depressed patients with comorbid OCD who have been treated with SSRIs. Demal et al[83] did find that in 24 depressed patients, there was a significant correlation between HAM-D scores and severity of OCD. In an open trial of fluoxetine with 61 patients with OCD, Jenike et al[84] found a significant decline in Beck depression scores over the 12-week trial. There was a significant improvement as indicated by the Yale-Brown obsessive-compulsive scale in both patients with (N=42) and without (N=19) concurrent depression. Cottraux et al[86] (1990) treated patients suffering from OCD, most of whom had some depressed mood (mean HAM-D=19), with fluvoxamine (with and without exposure therapy) or placebo with exposure therapy. All three groups had a decrease in both depression and rituals. In the first 8 weeks, fluvoxamine significantly decreased Beck depression scores and ritual duration. However, by week 24, there was only a non-significant superiority of fluvoxamine and exposure therapy and there were no between-group differences by week 48. Baseline depression scores only weakly predicted outcome of rituals with fluvoxamine and was unrelated to outcome for the group treated with placebo and exposure therapy.

Interestingly, there has been some question as to whether SSRIs, specifically fluoxetine, can actually aggravate or precipitate depression in patients with OCD. Hollander et al[86] report on 10 outpatients with OCD, some of whom appear to have had exacerbations of depression symptoms with fluoxetine treatment. In 6 patients, depressive symptoms developed when fluoxetine was rapidly increased. Eight patients had improvement of depressive symptoms when a TCA was added to fluoxetine. They also note that depressive and obsessive-compulsive symptoms do not always respond equally to fluoxetine and may be dissociated.

Alcohol

The efficacy of SSRIs in treatment of primary alcohol dependence is discussed in Chapter 5. However, there have been few studies of patients who carry the dual diagnosis of depression and alcohol dependence. Studies using TCAs in this population have generally found them to be ineffective, although increased drug metabolism in this patient population may have led to sub-optimal dosing and raises questions of methodological weaknesses.[87] In the first controlled study using a SSRI in patients with both alcohol dependence and depression, Cornelius et al[87] report on 21 inpatients. Alcohol consumption during the 12-week study was significantly lower in the fluoxetine group than in the placebo group. While the fluoxetine group had improvement on the Hamilton rating scale for depression-24 item (HAM-D-24) and the Beck depression inventory (BDI) scores, this was not a significant difference, likely due to the small sample size.

Panic

There is a high comorbidity of panic symptoms in patients with major depression but surprisingly few studies have been done with patients with both major depression and panic symptoms treated with SSRIs. Louie et al[88] studied 133 outpatients with major depression

in an open trial with fluoxetine (5-20 mg/day). They found that 20% (27/135) of the patients also met the criteria for panic disorder. These patients were much less likely to tolerate the full dose of 20 mg/day of fluoxetine (only 48% tolerated 20 mg/day) and were more likely to discontinue it altogether. Another study, treating patients with panic disorder and sub-syndromal depression with fluvoxamine and cognitive therapy, found that both depressive symptoms and panic symptoms improved at similar rates.[89] They also did not find an association between baseline depression score and remission of panic symptoms.

While antidepressants have been found to be helpful in both panic disorder and depression, there has been a question of whether treatment with a SSRI could paradoxically exacerbate depressive symptoms. Fux et al[90] report on 80 patients with panic disorder who received fluovoxamine (50-200 mg/day). Nine percent (7/80) of these patients developed depressive symptoms despite good anti-anxiety response and no previous history of affective illness. In these patients, depressive symptoms abated after fluvoxamine was discontinued and either a TCA or clonazepam were used. Five patients were later tried on fluoxetine (mean dose 20 mg/day) and all redeveloped depressive symptoms. In another group of 150 patients treated with TCAs, no depressive symptoms developed in patients without previous histories of affective illness.

Conclusion

Each of the manufacturers of the SSRIs would like to maintain that their product is both unique and superior to the competing SSRIs. As reviewed above, some differences do exist between these drugs, but the differences appear to be minor when compared to similarities.

References

1. Danish University Antidepressant Group. Citalopram: Clinical effect profile in comparison with clomipramine. A controlled multicenter study. Psychopharmacology 1986; 90:31-138.
2. Danish University Antidepressant Group. Paroxetine: A selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. J Affect Disord 1990; 18:289-299.
3. Nierenberg AA. The treatment of severe depression: Is there an efficacy gap between SSRI and TCA antidepressant generations? J Clin Psychiatry 1994; 55(Suppl):55-59.
4. Perry PJ. Pharmacotherapy for major depression with melancholic features: relative efficacy of tricyclic versus selective serotonin reuptake inhibitor antidepressants. J Affect Disord 1996; 39:1-6.
5. Roose SP, Glassman AH, Attia E et al. Comparative efficacy of selective serotonin reuptake inhibitors and tricyclics in the treatment of melancholia. Am J Psychiatry 1994; 151:1735-1739.
6. Finley PR. Selective serotonin reuptake inhibitors: Pharmacologic profiles and potential therapeutic distinctions. Ann Pharmacother 1994; 28:1359-1369.
7. Montgomery SA, Henry J, McDonald G et al. Selective serotonin reuptake inhibitors: Meta-analysis of discontinuation rates. Int Clin Psychopharmacol 1994; 9:47-53.
8. Song F, Freemantle N, Sheldon TA et al. Selective serotonin reuptake inhibitors: Meta-analysis of efficacy and acceptability. Br Med J 1993; 306:683-687.
9. Simon GE, VonKorff M, Heiligenstein JH et al. Initial antidepressant choice in primary care. JAMA 1996; 275:1897-1902.
10. George MS, Lydiard RB. Speed of onset of action of the newer antidepressants—fluoxetine and bupropion. Int Clin Psychopharmacol 1991; 6:209-217.
11. Dunbar GC, Cohn JB, Fabre LF et al. A comparison of paroxetine and placebo in the treatment of depressed outpatients. Br J Psychiatry 1991; 159:394-398.
12. Workman EA, Short DD. Atypical antidepressants versus imipramine in the treatment of major depression: A meta-analysis. J Clin Psychiatry 1993; 54:5-12.

13. Haria M, Fitton A, McTavish D. Trazodone. Drugs & Aging 1994; 4:331-355.
14. Falk WE, Rosenbaum JF, Otto MW et al. Fluoxetine versus trazodone in depressed geriatric patients. J Geriatr Psychiatry Neurol. 1989; 2:208-214.
15. Beasley Jr. CM, Dornseif BE, Pultz JA et al. Fluoxetine versus trazodone: Efficacy and activating-sedating effects. J Clin Psychiatry 1991; 52:294-299.
16. Perry PJ, Garvey MJ, Kelly MW et al. A comparative trial of fluoxetine versus trazodone in outpatients with major depression. J Clin Psychiatry 1989; 50:290-294.
17. Debus JR, Rush AJ, Himmel C et al. Fluoxetine versus trazodone in the treatment of outpatients with major depression. J Clin Psychiatry 1988; 49:422-426.
18. Hellerstein DJ, Yanowitch P, Rosenthal J et al. Long-term treatment of double depression: A preliminary study with serotonergic antidepressants. Prog Neuropsychopharmacol Biol Psychiatry 1994; 18:139-147.
19. Feiger A, Kiev A, Shrivastava RK et al. Nefazodone versus sertraline in outpatients with major depression: Focus on efficacy, tolerability, and effects on sexual function and satisfaction. J Clin Psychiatry 1996; 57(Suppl 2):53-62.
20. Baldwin DS, Hawley CJ, Abed TR et al. A multicenter double-blind comparison of nefazodone and paroxetine in the treatment of outpatients with moderate-to-severe depression. J Clin Psychiatry 1996; 57(Suppl 2):46-52.
21. Preskorn SH. Comparison of the tolerability of bupropion, fluoxetine, imipramine, nefazodone, paroxetine, sertraline and venlafaxine. J Clin Psychiatry 1995; 56(Suppl 6):12-21.
22. Dierick M, Ravizza L, Realini R et al. A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. Prog Neuropsychopharmacol Biol Psychiatry 1996; 20:57-71.
23. Clerc GE, Ruimy P, Verdeau-Pailles J. A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. Int Clin Psychopharmacol 1994; 9:139-143.
24. Kasper S. Clinical efficacy of mirtazapine: A review of meta-analyses of pooled data. Int Clin Psychopharmacol 1995;10 (suppl 4):25-35.
25. Stimmel GL, Dopheide JA, Stahl SM. Mirtazapine: An antidepressant with noradrenergic and specific serotonergic effects. Pharmacother 1997, 17:10-21.
26. Pande AC, Birkett M, Fechner-Bates S et al. Fluoxetine versus phenelzine in atypical depression. Biol Psychiatry 1996; 40: 1017-1020.
27. Williams R, Edwards RA, Newburn GM et al. A double-blind comparison of moclobemide and fluoxetine in the treatment of depressive disorders. Int Clin Psychopharmacol 1993, 7:155-158.
28. Lonnqvist J, Sintonen H, Syvalahti E et al. Antidepressant efficacy and quality of life in depression: a double-blind study with moclobemide and fluoxetine. Acta Psychiatr Scand 1994: 89:363-369.
29. Geretsegger C, Bohmer F, Ludwig M. Paroxetine in the elderly depressed patient: Randomized comparison with fluoxetine of efficacy, cognitive and behavioural effects. Int Clin Psychopharmacol 1994; 9:25-29.
30. Zanardi R, Franchini L, Gasperini M et al. Double-blind controlled trial of sertraline versus paroxetine in the treatment of delusional depression. Am J Psychiatry 1996; 153:1631-1633.
31. Schone W, Ludwig M. A double-blind study of paroxetine compared with fluoxetine in geriatric patients with major depression. J Clin Psychopharmacol 1993; 13(Suppl 2):34S -39S.
32. Newhouse PA, Richter EM. SSRIs in depressed elderly: A double-blind comparison of sertraline and fluoxetine in depressed geriatric outpatients (abstract). Eur Neuropsychopharmacol 1994; 4:332-333.
33. Aguglia E, Casacchia M, Cassano GB et al. Double-blind study of the efficacy and safety of sertraline versus fluoxetine in major depression. Int Clin Psychopharmacol 1993; 8:197-202.
34. de Wilde J, Spiers R, Mertens C et al. A double-blind, comparative, multicentre study comparing paroxetine with fluoxetine in depressed patients. Acta Psychiatr Scand 1993; 87:141-145.
35. Gagiano CA. A double blind comparison of paroxetine and fluoxetine in patients with major depression. Br J Clin Res 1993; 4:145-152.

36. Tignol J. A double-blind, randomized, fluoxetine-controlled, multicenter study of paroxetine in the treatment of depression. J Clin Psychopharmacol 1993; 13(Suppl 2):18S-22S.
37. Ansseau M, Gabriels A, Loyens J et al. Controlled comparison of paroxetine and fluvoxamine in major depression. Hum Psychopharmacol 1994; 9:329-336.
38. Montgomery SA, Johnson FN Citalopram in the treatment of depression. Rev Contemp Pharmacother 1996; 6:297-306.
39. Ontiveros A, Garcia-Barriga C. A double-blind, comparative, multicentre study comparing paroxetine with fluoxetine in depressed patients (abstract). Biol Psychiatry 1994; 35:667.
40. Bennie EH, Mullin JM, Martindale JJ. A double-blind multicenter trial comparing sertraline and fluoxetine in outpatients with major depression. J Clin Psychiatry 1995; 56:229-237.
41. Nemeroff CB, Ninan PT, Ballenger JC. Double-blind multicentre comparison of fluvoxamine versus sertraline in the treatment of depressed outpatients. Depression 1995; 3:163-169.
42. Van Moffaert M, Bartholeme F, Cosyns P et al. A controlled comparison of sertraline and fluoxetine in acute and continuation treatment of major depression. Hum Psychopharmacol 1995; 10:393-405.
43. Haffmans PMJ, Timmerman L, Hoogduin CAL. Lucifer Group. Efficacy and tolerability of citalopram in comparison with fluvoxamine in depressed outpatients: A double-blind, multicentre study. Int Clin Psychopharmacol 1996; 11:331-355.
44. Rapaport M, Coccaro E, Sheline Y et al. A comparison of fluvoxamine and fluoxetine in the treatment of major depression. J Clin Psychopharmacol 1996; 16:373-378.
45. Franchini L, Gasperini M, Perez J et al. A double-blind study of long-term treatment with sertraline or fluvoxamine for prevention of highly recurrent unipolar depression. J Clin Psychiatry 1997; 58:104-107.
46. Kiev A, Feiger A. A double-blind comparison of fluvoxamine and paroxetine in the treatment of depressed outpatients. J Clin Psychiatry 1997; 58:146-152.
47. Brown WA, Harrison W. Are patients who are intolerant to one SSRI intolerant to another? Psychopharmacol Bull 1992; 28:253-256.
48. Liu BA, Mittmann N, Knowles SR et al. Hyponatremia and the syndrome of inappropriate secretion of antidiuretic hormone associated with the use of selective serotonin reuptake inhibitors: A review of spontaneous reports. Can Med Assoc J 1996; 155:519-527.
49. Leo RJ. Movement disorder associated with the SSRIs. J Clin Psychiatry 1996; 57:449-454.
50. Balon R, Yergani VK, Pohl R et al. Sexual dysfunction during antidepressant treatment. J Clin Psychiatry 1993; 54:209-212.
51. Modell JG, Katholi CR, Modell JD et al. Comparative sexual side-effects of bupropion, fluoxetine, paroxetine, and sertraline. Clin Pharmacol Ther 1997; 61:476-487.
52. DeVane CL. Pharmacokinetics of the selective serotonin reuptake inhibitors. J Clin Psychiatry 1992; 53(Suppl 2):13-20.
53. Baumann P, Larsen F. The pharmacokinetics of citalopram. Rev Contemp Pharmacotherapy 1995; 6:287-295.
54. van Harten J. Clinical pharmacokinetics of selective serotonin reuptake inhibitors. Clin Pharmacokinetics 1993: 24:203-20.
55. Altamura AC, Moro AR, Percudani M. Clinical Pharmacokinetics of fluoxetine. Clin Pharmacokinetics 1994; 26:201-214.
56. Mallya G, White K, Gunderson C. Is there a serotonergic withdrawal syndrome? Biol Psychiatry 1993; 33:849-850.
57. Heiligenstein JH, Tollefson GD, Faries DE. Response patterns of depressed outpatients with and without melancholia: A double-blind, placebo-controlled trial of fluoxetine versus placebo. J Affect Disord 1994; 30:163-173.
58. Gravem A, Amthor F, Astrup C et al. A double-blind comparison of citalopram and amitriptyline in depressed patients. Acta Psychiatr Scand 1987; 75:478-486.
59. Ginestet D. Fluoxetine in endogenous depression and melancholia versus clomipramine. Int Clin Psychopharmacol 1989; 4(Suppl 1):37-40.
60. Nielsen OA, Morsing I, Petersen JS et al. Paroxetine and imipramine treatment of depressive patients in a controlled multicentre study with plasma amino acid measurements. Acta Psychiatr Scand 1991; 84:233-241.

61. Feighner JP, Boyer WF, Meredith CH et al. A placebo-controlled inpatient comparison of fluvoxamine maleate and imipramine in major depression. Int Clin Psychopharmacol 1989; 4:239-244.
62. Liebowitz MR. Depression with anxiety and atypical depression. J Clin Psychiatry 1993; 54 (suppl): 10-14
63. Nierenberg AA, Pava JA, Clancy K et al Are neurovegetative symptoms stable in relapsing or recurrent atypical depressive episodes? Biol Psychiatry 1996; 40:691-696.
64. Fava M, Rosenbaum JF, Pava JA et al. Anger attacks in unipolar depression, part 1: Clinical correlates and response to fluoxetine treatment. Am J Psychiatry 1993; 150:1158-1163.
65. Fava M, Nierenberg AA, Quitkin FM et al. A preliminary study on the efficacy of sertraline and imipramine on anger attacks in atypical depression and dysthymia. Psychopharmacol Bull 1997; 33:101-103.
66. Syvalahti EKG, Kallioniemi H, Lehto H. Citalopram in patients with unsatisfactory response to neuroleptics: An open follow-up study. Methods and Finding. Exp Clin Pharmacology 1994, 16: 49-55.
67. Clayton PJ, Grove WM, Coryell W et al. Follow-up and family study of anxious depression. Am J Psychiatry 1991; 148:1512-1517.
68. Flint AJ, Rifat SL. Anxious Depression in elderly patients. Am J Geriatr Psychiatry 1997; 5:107-115.
69. Burns RA, Lock T, Edwards DRL et al. Predictors of response to amine-specific antidepressants. J Affect Disord 1995; 35:97-106.
70. Sheehan D, Dunbar GC, Fuell DL. The effect of paroxetine on anxiety and agitation associated with depression. Psychopharmacol Bull 1992; 28:139-143.
71. Tollefson GD, Greist JH, Jefferson JW et al. Is baseline agitation a relative contraindication for a selective serotonin reuptake inhibitor: A comparative trial of fluoxetine versus imipramine. J Clin Psychopharmacol 1994; 14:385-391.
72. Ravindran AV, Judge R, Hunter BN et al. A double-blind, multicenter study in primary care comparing paroxetine and clomipramine in patients with depression and associated anxiety. J Clin Psychiatry 1997; 58:112-118.
73. Tollefson GD, Holman SL, Sayler ME et al. Fluoxetine, placebo and tricyclic antidepressants in major depression with and without anxious features. J Clin Psychiatry 1994; 55:50-59.
74. Dunbar GC, Fuell DL. The anti-anxiety and anti-agitation effects of paroxetine in depressed patients. Int Clin Psychopharmacol 1992; 6(Suppl 4):81-90.
75. Stoll AL, Mayer PV, Kolbrener M et al. Antidepressant-associated mania: A controlled comparison with spontaneous mania. Am J Psychiatry 1994; 51:1642-1645.
76. Peet M. Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. Br J Psychiatry 1994; 164:549-550.
77. Sachs GS, Lafer B, Stoll AL et al. A double-blind trial of bupropion versus desipramine for bipolar depression. J Clin Psychiatry 1994; 55:391-393.
78. Simpson SG, DePaulo JR. Fluoxetine treatment of bipolar II depression. J Clin Psychopharmacol 1991; 11:52-54.
79. Cohn JB, Collins G, Ashbrook E et al. A comparison of fluoxetine imipramine and placebo in patients with bipolar depressive disorder. Int Clin Psychopharmacol 1989; 4:313-322.
80. Rothschild AJ, Samson JA, Bessette MP et al. Efficacy of the combination of fluoxetine and perphenazine in the treatment of psychotic depression. J Clin Psychiatry 1993; 54:338-342.
81 Gatti F, Bellini L, Gasperini M et al. Fluvoxamine alone in the treatment of delusional depression. Am J Psychiatry 1996; 153:414-416.
82. Kasper S, Fuger J, Moller HJ. Comparative efficacy of antidepressants. Drugs 1992; 43(Suppl 2):11-23.
83. Demal U, Zitterl W, Lenz G et al. Obsessive compulsive disorder and depression-first result of a prospective study on 74 patients. Prog Neuropsychopharmacol Biol Psychiatry 1996; 20:801-813.
84. Jenike MA, Buttolph L, Baer L et al. Open trial of fluoxetine in obsessive-compulsive disorder. Am J Psychiatry 1989; 146:909-911.

85. Cottraux J, Mollard E, Bouvard M et al. A controlled study of fluvoxamine and exposure in obsessive-compulsive disorder. Int Clin Psychopharmacol 1990; 5:17-30.
86. Hollander E, Mullen L, DeCaria CM et al. Obsessive compulsive disorder, depression, and fluoxetine. J Clin Psychiatry 1991; 52:418-422.
87. Cornelius JR, Salloum IM, Cornelius MD et al. Preliminary report: Double-blind, placebo-controlled study of fluoxetine in depressed alcoholics. Psychopharmacol Bull 1995; 31:297-303.
88. Louie AK, Lewis TB, Lannon RA. Use of low-dose fluoxetine in major depression and panic disorder. J Clin Psychiatry 1993; 54:435-438.
89. Black DW, Wesner R, Bowers W et al. Acute treatment response in outpatients with panic disorder: High versus low depressive symptoms. Ann Clin Psychiatry 1995; 7:181-188.
90. Fux M, Taub M, Zohar J. Emergence of depressive symptoms during treatment for panic disorder with specific 5-hydroxytryptophan reuptake inhibitors. Acta Psychiatr Scand 1993; 88:235-237.

Chapter 4

SSRIs and Patient Groups with Specific Treatment Problems

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Selective serotonin reuptake inhibitors (SSRIs), whilst initially launched solely as antidepressants, have been used increasingly as treatments for other disorders and in patients who are vulnerable to the adverse effects of other antidepressants. This chapter examines the role of SSRIs in two groups of patients whose age places them in the latter category (the young and the elderly), concentrating on the management of a number of psychiatric disorders specific to them. Also discussed is the efficacy of SSRIs in other groups of patients in which these compounds may turn out to be a particularly useful form of therapy.

Children and Adolescents

Specific Problems of Psychopharmacology in the Young

It seems particularly germane at this time, given the British Association for Psychopharmacology consensus statement of 1997,[1] to consider this group of patients. The child and adolescent psychiatrist has specific problems to contend with. In particular, many diagnostic categories are at the descriptive level of symptom groupings, even more so than with the rest of psychiatry. The influence of development means that what may be 'normal' in early childhood can be considered as 'pathological' at a later stage of development. Many disorders have important social and environmental factors and so thorough multi-speciality assessment regarding diagnosis and treatment is necessary. While the place of pharmacotherapy in the management of childhood psychiatric disorders is still debated, the advent of the SSRIs has added an exciting therapeutic opportunity. However, despite the obvious benefits of SSRIs within adult psychiatry, an extrapolation to child psychiatry is limited and a cautious approach is generally justified by concerns about toxic side-effects and potential effects on growth and development.[2]

Before any pharmacodynamic and pharmacokinetic differences can be taken into consideration, it has to be remembered that ensuring compliance with medication is even more important than with adults. Often, several people need to be fully involved including the child, their parents, teachers and others. Clear explanations regarding rationale, side-effects and dosage schedules are needed and any fears must be allayed and all questions answered. There are specific pharmacodynamic and pharmacokinetic differences unique to early stages of development. Although factors such as gastric pH, gut flora and gut wall metabolism vary with age and can theoretically affect absorption, these variations cause little observed difference in absorption from childhood to adult life.[3] However, the increased use of liquid formulations in pediatric practice leads to a more rapid rate, but not extent, of

Selective Serotonin Reuptake Inhibitors (SSRIs): Past, Present and Future,
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absorption with increased risk of toxic effects. The bioavailability and percentage of the administered dose which reaches the circulation seems to be similar in children and adults. Younger children have more active metabolism with liver tissue capable of the same metabolizing capacity as adults but they have a larger liver mass/body mass ratio. This leads to more rapid oxidation, reduction and hydroxylation which steadily approaches adult levels in adolescence.[4]

The distribution of agents is affected by many factors that change with age, i.e., rate of absorption, membrane penetration, perfusion, volume and the composition of tissue compartments as well as the extent of binding to protein and tissues. Some of these factors have implications for agent dosing (intra-/extracellular water to total body water ratio, body fat levels): for most drugs, the younger the child the larger the weight-related dose necessary. As surface-area-related values for glomerular filtration reach adult values at around 5 months, this causes little limitation to medication use unless renal function is compromised. Inter-subject variation is seen with children of similar ages showing differing rates of drug bio-transformation, but there is a less marked difference in renal elimination.[4]

While it seems possible that there are age-related receptor differences between children at different developmental levels, there is little in vivo research to confirm this. The effects of amphetamines in children could hardly have been predicted from their effects in adults[5,6] and fluoxetine can produce side-effects in children, not commonly seen in adults, such as restlessness and social disinhibition.[7,8]

Obsessive-Compulsive Disorder

The most convincing evidence for the use of SSRIs in this group is in obsessive-compulsive disorder (OCD), and this would concur with the evidence for serotonergic dysfunction in this disorder. Fluoxetine is the SSRI most studied in this area but unfortunately there are very few trials. The only published randomized, double-blind, placebo-controlled trial involved a fixed dose of fluoxetine (20 mg/day) in 14 patients with OCD (aged 8-15 years).[8] The study, which lasted for 20 weeks with a crossover at 8 weeks, used the Yale-Brown obsessive-compulsive scale (Y-BOCS) and the Clinical Global Impressions (CGI) scale. A statistically significant improvement was found in the CGI, though the decrease in Y-BOCS in the active treatment group (44%) was not statistically significant when compared with the placebo group (27%) after the initial 8 weeks of active treatment. While full details are not yet available, a preliminary report of a placebo-controlled trial of fluvoxamine in pediatric outpatients[9] shows fluvoxamine's superiority to placebo with the best improvement occurring in 8-11 year-olds. Prospective open trials using fluoxetine[7] and fluvoxamine[10] have shown more positive results. Riddle et al[7] found improvements in CGI and Y-BOCS in 50% of the patients with primary OCD though the numbers were very small. Apter et al,[10] in an 8-week, open-label trial of fluvoxamine, treated 20 adolescent inpatients for OCD (N=14) or major depressive disorder. They found a significant improvement in Y-BOCS after 6 weeks. In the study of Geller et al[11] which used retrospective ratings of 38 prepubertal OCD patients' charts, 28 (74%) showed moderate to marked improvement of OCD symptoms with fluoxetine over an average follow-up period of 19 months. Several case reports agree that fluoxetine alone or in combination is of benefit in individual cases of patients with OCD. [12-14]

Depressive Disorder

The efficacy and tolerability of SSRIs in the adult depressed population is well documented and has been described in earlier chapters (see: Chapters 2 and 3). The number of trials in children and adolescents is limited and their outcome complicated by a high placebo response rate. Simeon et al[15] performed a double-blind placebo-controlled trial in

40 13 -18 year-olds with depression using fluoxetine. Of the 32 patients at 8 week follow-up, symptom scores had improved from baseline with significant levels being reached at 3 weeks. The fluoxetine group showed greater improvement in the majority of clinical variables but this was not statistically significant. Apter et al,[10] as reported above, found fluvoxamine effective in depression as judged by the Beck Depression Inventory (BDI) and Colle et al[16] studied 9 adolescents (aged 15-18) and showed that short duration of illness improved treatment response significantly. The authors also found that prolonging fluoxetine treatment increased the apparent response in those patients with long illness duration. Rodriguez-Ramos et al[17] and Jain et al[18] showed treatment response in over half the subjects, using open-label paroxetine and fluoxetine respectively, in retrospective studies. Boulos et al[19] reported an open study of 15 adolescents who had been resistant to prior tricyclic antidepressant therapy. Of the 11 patients who completed the trial of fluoxetine, 64% showed greater than a 50% change in the Hamilton rating scale for depression (HAM-D).

Tourette's Syndrome

Obsessive-compulsive behaviors (OCB) occur in more than 50% of patients with the Gilles de la Tourette syndrome (GTS) and it is hardly surprising that trials in GTS have mainly focused on obsessive-compulsive and 'other symptoms.' The only double-blind, controlled clinical trial used fluoxetine (20-40 mg/day) and placebo in 11 children with Tourette's syndrome and associated obsessive-compulsive symptoms (OCS) over a 4 month period.[20] Fluoxetine therapy was associated with a non-significant trend towards improvement in tic severity, attentional abilities and social functioning. The authors were unable to replicate an earlier open study of fluoxetine[21] which reported a significant reduction in scores on the Leyton Obsessional Inventory (LOI). An improvement in obsessional symptoms was also found by Riddle et al[7] in a subgroup of GTS patients with OCD treated with open-label fluoxetine for 20 weeks. Eapen et al[22] reported on their clinical experience of fluoxetine in 30 GTS patients with OCB, in an open retrospective study in which most patients were receiving fluoxetine (20-40 mg/day) for an average of 6 months. There was an overall improvement in OCB as judged by the clinician in 76% of subjects. One case report of the use of sertraline and pimozide in GTS describes decreased motor and vocal tics and obsessions in a 15 year-old girl.[23]

Autistic Disorder

As pointed out by Kaplan and Hussain,[2] the main role of medication in autism is in the management of symptoms. The only trial of SSRIs in this population was open-labelled using fluoxetine in 23 7-28 year-olds, 21 of whom had some degree of mental retardation.[24] Fifteen of the 23 showed significant improvement on the CGI scale, though 13 were receiving concomitant psychotropic medication. Individual case reports have provided mixed results.[25-28] Ghaziuddin et al[25] found that the greatest improvement was when depressive illness was present, emphasizing the need for controlled trials.

Hyperkinetic Disorder

Biochemical research into neurotransmitters in this disorder has increased interest in drug treatments for these conditions.[29] However, the use of psychostimulants for this heterogeneous group of behavior disorders differs markedly between the UK and the USA,[30,31] with medication use much higher in the USA. Two open studies have used SSRIs in this group. Barrickman et al[32] found that of the 19 (86%) patients completing their trial of fluoxetine (20-60 mg/day), 58% showed improvement with most obtaining 'moderate' benefit. The subjects were regarded as treatment-resistant by history, some had previously been taking psychostimulants and a few were taking psychoactive treatments. Gammon

and Brown[33] reported a trial of 'add on therapy' (to methylphenidate) using fluoxetine (up to 20 mg/day) in 32 patients aged 9-17 years. 94% of patients showed significant improvement on rating scales as well as gains in school performance.

In summary, although open studies and limited double-blind trials of SSRIs appear to show promise in a number of conditions in child and adolescent psychiatry, unequivocal evidence is still lacking. The paucity of evidence especially in the form of large, randomized, double-blind, placebo-controlled trials is regrettable and cautions against widespread use of SSRIs in children. While the most convincing evidence is for efficacy in depression and obsessive-compulsive disorder, clinicians must be aware that the present use of SSRIs in children is not recommended on the UK data sheets of all this class of drug (although this is not the case in the USA).

Bulimia Nervosa

The finding that non-depressed bulimic patients respond to pharmacotherapy with antidepressant drugs suggested that these compounds may have a specific use in the treatment of the symptoms of bulimia nervosa.[34] The demonstration of the role of serotonergic neurons in the regulation of appetite and satiety provided a scientific base to underpin this.[35] The positive finding of Freeman and Hampson[36] in their early open-label trial of fluoxetine paved the way for larger more formal evaluations of efficacy. The Fluoxetine Bulimia Nervosa Collaborative Study Group[37] performed an 8 week, double-blind trial comparing fluoxetine (20 and 60 mg/day) with placebo in 387 bulimic female outpatients. They found significant dose-dependent effects of active treatment in reducing the frequency of weekly binge-eating and vomiting, depression, carbohydrate craving, eating attitudes and behaviors at the end point. This dose response was also found in the reports of adverse events: these occurring significantly more frequently with fluoxetine than with placebo. In a study of longer-term (16 week) use of fluoxetine in the same group Goldstein et al[38] studied the effect of active treatment of 398 randomized bulimic patients (225 completed). Active treatment resulted in significantly greater reductions in vomiting and binge-eating episodes, while treatment was well tolerated and safe.

Other SSRIs such as sertraline[39] and fluvoxamine have been used but not studied to the same extent as fluoxetine. Ayuso-Gutierrez et al[40] reported an open trial of fluvoxamine in 20 patients with bulimia nervosa and concluded that it was a safe and effective treatment for bulimia nervosa. Brambilla and colleagues,[41] in a naturalistic study of 15 patients, examined the effect of fluvoxamine combined with cognitive-behavioral and nutritional therapy. They found no difference between the two drug-treatment groups (amantidine and fluvoxamine). Comprehensive reviews[42,43] have concluded that all antidepressants studied appear to be effective in this condition, especially in relation to bingeing and vomiting. Boyer and Feighner[43] reported a highly significant relationship between dose of SSRI and reduction of bingeing which was still present even when studies of fluoxetine were excluded.

In summary, although the common mode of action of SSRIs would suggest they are all likely to be effective in bulimia, real evidence of efficacy is only available for fluoxetine and fluvoxamine. Few data are available regarding the long-term outcome of patients and some concerns have been raised over relapse following medication discontinuation.[44] Despite reservations it is important to remember Herzog and Sacks'[45] findings that bulimic patients who had drug treatment within the first 13 weeks of onset were more likely to demonstrate sustained recovery over the course of the first year.

Anorexia Nervosa

Given the similarity in psychopathology in bulimia nervosa and anorexia nervosa, combined with pre-clinical findings that serotonin (5-hydroxytryptamine, 5-HT) has anorectic properties,[46] it is not surprising that SSRIs have been suggested as a therapeutic option for the latter condition. Although the weight loss associated with SSRIs may present a theoretical problem, their usefulness has been reported in individual patients[47] and in trials.[41,48,49] Gwirtsman et al[48] found that fluoxetine reduced depressive symptoms and increased weight gain in an open trial of 6 treatment-refractory patients. Patients tolerated the treatment despite the sometimes high doses used (up to 60 mg/day) though it was not clear how much the weight gain was a function of improvement in mood rather than a specific anti-anorectic action. In another open study of 31 weight-restored anorexic outpatients, Kaye et al[49] found fluoxetine helped maintain body weight, although it should be noted that increased baseline depression scores were a predictor of poor response. Open trials in this area are particularly difficult to interpret because of the concurrent psychotherapeutic approach which is universally used with such patients. Brambilla and colleagues[41] compared the effects of amineptine and fluoxetine in different subtypes of anorexia. Their four-month trials of combined cognitive-behavioral, nutritional and antidepressant therapy studied two cohorts: anorexia nervosa, restricted type (N=22) and anorexia nervosa, binge-eating/purging type (N=13). No difference was found between treatment groups, though both treatments produced significant improvements in body mass index (BMI), depression, anxiety and score on the Eating Disorders Inventory.

In summary, while open studies have been encouraging, to date no double-blind placebo-controlled trials have been reported that confirm or refute the efficacy of SSRIs in this patient group.

Premenstrual Syndromes

Estimates in women with regular menstrual periods suggest that up to 75% have symptoms of premenstrual syndrome (PMS),[50] though the vast majority do not require medical or psychiatric treatment. The recognition of severe symptoms in some women has been helped with the inclusion of late luteal phase dysphoric disorder (LLPDD) and premenstrual dysphoric disorder (PMDD) in the DSM III-R[51] (for the former) and DSM IV.[52] PMDD affects 3-8% of women of reproductive age having symptoms which interfere with lifestyle and relationships and appears not to respond to conservative and conventional treatments.[53] 5-HT may be linked with the pathophysiology of PMDD[54] and SSRIs have been tried as treatment.

The majority of early work was conducted using fluoxetine and, following the success of fluoxetine in PMS found by Stone et al,[55] the same authors published results of a double-blind randomized placebo-controlled trial in 20 women with LLPDD.[56] The active treatment was highly significantly superior to placebo and interestingly all patients receiving fluoxetine elected to continue with this treatment after the completion of the study. Wood et al[57] and more recently Su et al[58] confirmed these findings in a double-blind placebo-controlled crossover study in 8 and 17 women respectively, with Wood finding it to be a well-tolerated treatment. There are other reports of effectiveness in open trials.[59,60] A large multi-center trial (180 completing) reported by Steiner et al[61] confirmed previous positive results of fluoxetine. A dose of 20 mg/day was effective and increasing this to 60 mg/day only increased the likelihood of side-effects. Continuous administration is necessary during the menstrual cycle and unfortunately symptoms seem to recur on discontinuation of medication.[61,62]

Recently Yonkers et al[63] reported a large multi-center placebo-controlled trial of sertraline in women with PMDD. Sertraline produced significant improvement in daily symptoms and depression scores in comparison with placebo. Eriksson et al,[64] in a blind

comparison of paroxetine to maprotiline and placebo, found paroxetine superior to the other groups.

In summary, both open and double-blind studies support the efficacy of SSRIs in PMDD and, although most of the evidence is for fluoxetine and sertraline, it seems likely that this is a class effect.

Impulse-Control Disorders

Impairments of impulse control are seen in many psychiatric and neurological disorders and as resulting behaviors, such as aggression, may cause conflict with society they present an important potential use for SSRIs, although not a currently licensed one. There is now a body of literature exploring the relationship between 5-HT and aggression/impulsive behaviors in both animals and humans. Mehlman et al[65] measured the concentration of the 5-HT metabolite, 5-hydroyindoleacetic acid (5-HIAA), in the cerebrospinal fluid (CSF) of 26 free-ranging adolescent male primates (*Rhesus macaques)* during routine capture and medical examination. They found an inverse correlation between the concentration of CSF 5-HIAA and the exhibiting of more violent forms of aggressive behavior and loss of impulse control. Similarly, Hingley et al[66] found a negative correlation between CSF 5-HIAA concentrations and impulsive behavior and severe unrestrained aggression, but not with overall rates of aggression. They concluded that, in non-human primates at least, low 5-HT release lowers the threshold for impulsive action and that, when provoked by an appropriate stimulus, this can result in unrestrained aggression.

Experimental work in humans with impulse control problems[67] suggests that extrapolation of this work to humans may be appropriate. Coccaro showed a decreased prolactin response to administration of the 5-HT releasing agent, *d*-fenfluramine, in patients with mood and/or personality disorder, especially in those with a history of parasuicide and impulsive aggression and a diagnosed personality disorder. His group, along with others,[68,69] have postulated that there is decreased postsynaptic sensitivity to 5-HT in this group of patients. Recent work by Coccaro et al[70] demonstrated, in a double-blind placebo-controlled study, that the efficacy of fluoxetine in treating aggression is positively correlated with the magnitude of prolactin response to *d*-fenfluramine, perhaps reflecting altered postsynaptic sensitivity to 5-HT. The finding of reduced CSF concentrations of 5-HIAA in the CSF of patients with increased impulsivity and an inverse correlation between 5-HIAA and life-history measures of aggression also implicates a deficit in serotonergic transmission with increased impulsivity.[71]

As a result of such work there have been a number of open trials examining the therapeutic value of SSRIs in patient groups where aggressive behavior and emotional lability are seen. Coccaro et al[72] reported a diminution of aggression after fluoxetine treatment in 3 patients with impulsive aggression and a diagnosis of DSM-III-R personality disorder. Severe forms of aggression responded within the first one to two weeks while verbal aggression and irritability took longer. This led the authors to suggest that the primary role of 5-HT is in the mediation of impulsive behavior, while less severe impulsive behaviors may be associated with a less marked central 5-HT deficit. Kavoussi et al[73] treated 11 patients with a DSM-III-R diagnosis of personality disorder with sertraline in an open clinical trial with a flexible dosing schedule. Nine patients completed at least 4 weeks of the trial and seven completed 8 weeks. Significant improvement in irritability and overt aggression was observed at 4 weeks with continuing improvement through to week 8. Salzman et al[74] carried out one of the few double-blind placebo-controlled trials of SSRI use in aggression. They treated 21 patients with DSM-III-R borderline personality disorder with fluoxetine (20 mg/day) and found a reduction in overall distress with the most significant reduction seen in anger and aggression.

Fava et al have carried out a number of open studies[75-77] of fluoxetine treatment in depressed patients with what they have called 'anger attacks', finding a significant improvement in these attacks during drug treatment. They also examined the prolactin response to administration of thyrotropin-releasing hormone (TRH), finding that this was increased by fluoxetine treatment. Patients with the greatest prolactin response experienced a better response to treatment suggesting, perhaps, a greater degree of central serotonergic dysfunction in those depressed patients who had anger attacks.

Other conditions for which SSRIs have been advocated include emotional lability and 'pathological crying'. Some authors regard these two conditions as synonymous,[78] others propose that 'pathological crying' is a separate entity.[79] Within this chapter the latter usage has been adopted, although both have been considered as an impairment of impulse control. Mukand et al[80] reported on the efficacy of sertraline for treating pathological crying and laughing following stroke in two patients. They both showed significant improvement in these variables and staff also noted improvements in sleeping, eating, social interaction, and therapy participation. A double-blind, placebo-controlled study by Andersen et al[79] on the effects of citalopram (10-20 mg/day) on pathological crying found a rapid (1-3 day) and pronounced effect on the frequency of crying in 73% of a post-stroke population.

Sloan et al[81] treated six individuals with acquired brain injury with fluoxetine (20 mg/day) in an open trial. Five had suffered a cerebrovascular accident (CVA) and all had emotional lability. Within 1 week of commencing treatment marked improvement in emotional lability was seen in all 6 patients. Seliger et al[82] treated 13 patients with emotional lability (post-stroke or due to multiple sclerosis) over 12 months using fluoxetine (20 mg/day). Significant responses were seen within 3-14 days in all patients and were sustained for the period of treatment. On discontinuation, two patients had a relapse of emotional lability which resolved in one when fluoxetine was recommenced.

Previous studies of SSRI use in aggression and other impulse-control disorders suffer from several methodological difficulties such as the inclusion of heterogeneous samples of small size, the inclusion of subjects with significant comorbidity (e.g., combined mood and personality disorder), the lack of rigorous double-blind placebo-controlled studies and the use of variable doses for variable lengths of time. Promising preliminary evidence and the relatively low toxicity of SSRIs in comparison to other medications advocated for the treatment of impulse-control disorders makes further therapeutic trials with SSRIs of particular interest.

The Elderly

The increased vulnerability of elderly subjects to side-effects of tricyclic antidepressants, particularly cardiac problems, orthostatic hypotension, sedation and cognitive impairments often causes clinicians to consider the use of SSRIs as an alternative treatment to tricyclic antidepressants in the elderly. While a detailed discussion of pharmacokinetic and pharmacodynamic changes with aging is outside the scope of this chapter (but see: Chapter 2) it is important to note that some important differences exist between SSRIs. For example, some SSRIs show linear kinetics (citalopram and sertraline) while others do not. Age-related changes in plasma concentrations also vary, with fluvoxamine and sertraline showing little change with age while levels of citalopram and paroxetine may be double in the elderly. They also differ in their potency to inhibit different subtypes of the cytochrome P450 system, an important system involved in oxidative metabolism of many drugs. This results in slightly different possibilities for drug interactions for individual SSRIs.[83]

Depression

The evidence for treating depression in old age with SSRIs broadly mirrors that in younger patients. Studies, such as those reported by Gottfries, Karlsson and Nyth[84] which compared SSRIs with placebo, demonstrated a clear therapeutic benefit for the active drug over placebo. Gottfries et al[85] discussed citalopram treatment of depression in the elderly, based on two inter-Nordic studies, and concluded that citalopram was well tolerated and significantly improved emotional disturbances in patients with dementia and resulted in a significant improvement in the elderly depressed as measured by the HAM-D. The Fluoxetine Collaborative Study Group[86] reported a double-blind, placebo-controlled trial of fluoxetine (20 mg/day) in 671 elderly patients with major depression. After 6 weeks fluoxetine was found to be significantly more efficacious than placebo with regard to overall response and remission rates. Early discontinuations due to adverse drug events were not significantly different for fluoxetine and placebo.

A number of studies have compared SSRIs with other antidepressants.[87-90] These consistently show an equivalent antidepressant effect for both groups of drugs being compared but an advantage for the SSRIs was fewer side-effects such as sedation, weight gain and anticholinergic effects. The only exception was the Stuppaeck et al study.[90] This multi-center double-blind study of paroxetine and amitriptyline in 153 elderly depressed inpatients, as with the other studies, showed similar antidepressant responses but with overall adverse events distributed similarly in both the paroxetine and amitriptyline groups. Patients in the paroxetine group showed more anxiety and agitation, and anticholinergic side-effects were seen more often in those taking amitriptyline. In a study comparing the use of two SSRIs, paroxetine and fluoxetine, Geretsegger, Bohmer and Ludwig[91] carried out a 6-week, double-blind, randomized study of 106 elderly depressed patients. Similar efficacy in the treatment of depression was seen with both groups but, at the end of treatment, more patients in the fluoxetine group had withdrawn despite there being no apparent difference in either tolerability or safety between the two drugs. All measures of cognitive and behavioral function improved in both groups but, from week 3, paroxetine was significantly superior to fluoxetine, possibly suggesting an earlier response for paroxetine. Dunbar[92] performed a meta-analysis of 10 studies comparing paroxetine against standard antidepressant pharmacotherapy in elderly patients. Paroxetine was as effective an antidepressant as active controls while change in symptomatology, as measured by the HAM-D scale, over the first 5-6 weeks was significantly greater with paroxetine. The paroxetine group had less frequent and less severe adverse events, particularly anticholinergic side-effects. Paroxetine was also effective in treating anxiety symptoms associated with depression and caused significantly less sedation. Whilst little difference in the overall safety profiles was seen, data indicated reduced cardiotoxicity for paroxetine and a beneficial effect on suicidal thoughts. The authors concluded that the results indicated that paroxetine was an alternative first-line therapy to older antidepressants and should be considered when treating elderly patients.

A review by Schneider and Olin[93] points out that there is marked difficulty in comparing such trials as efficacy and side-effect rates for any particular medication vary between trials and that there is considerable variation in the drugs used in the trials, their dosages and trial design. Rightly, they caution against over-interpretation of results in light of this. Menting et al[94] in attempting to address this problem, carried out a qualitative analysis of the literature on the efficacy and side-effects of SSRIs in the treatment of elderly depressed patients. They examined placebo-controlled or comparison studies of SSRI versus other antidepressants. Sixteen studies were analyzed and, after assessment of methodological quality, six were reviewed. These studies found that all antidepressants were equally effective after the treatment periods (of 4-8 weeks). However, side-effects were different and occurred less frequently with SSRIs than with tricyclic antidepressants with fewer SSRI-treated patients

dropping out. No significant predictors of response to SSRIs in elderly depressives have been identified.[95,96] SSRIs have been advocated for treatment of dysthymia, though studies are limited.[97,98]

Depression and Dementia

In a double-blind randomized trial of amitriptyline versus fluoxetine Taragano et al[99] studied 37 patients with major depression complicating senile dementia of Alzheimer's type (SDAT). Significant improvements in HAM-D and Mini Mental State Examination (MMSE) ratings were observed in both groups completing treatment to day 45 but the groups were not significantly different from each other. A significant difference between groups was seen in the dropout rate: 58% of amitriptyline-treated patients dropped out as opposed to 22% treated with fluoxetine. The authors concluded that whilst there was no difference in the efficacy of the two drugs fluoxetine was better tolerated and the preferred drug in this group of patients. Nyth and Gottfries[100] reported on 98 demented patients, with either SDAT or multi-infarct dementia. They were treated with citalopram (10-30 mg/day) and at 4 weeks significant improvement in confusion, irritability, anxiety, depressed mood and restlessness was seen in the SDAT group (but not those with multi-infarct dementia). No effect on intellectual capacity or motor performance was measured in either group. Volicer, Rheaume and Cyr[101] examined the effect of treating depressed affect and food refusal, in 10 patients with advanced SDAT, with sertraline. The affect of 8 of the patients improved and a decrease in food refusal was seen in 5 of the 6 with this problem. In an open study into the use of citalopram in a heterogeneous group of 123 patients with symptoms of depression and/or anxiety Ragneskog et al[102] found significant reduction in symptoms in those patients who completed 12 months of treatment. The group examined contained 93 patients with dementia and only 52 (42%) of the original group completed 12 months treatment. Few side-effects were seen in any of the patients and those that occurred were mainly mild. In a more severe group of 20 patients with dementia complicated by depression and psychosis Burke et al[103] retrospectively examined their case notes. Twelve had SDAT, the remaining eight having other dementias, all had been treated with SSRIs. Fifteen had moderate to marked improvement in their depressive and psychotic symptoms (11 of these had SDAT). The SSRIs also proved effective in eliminating psychotic symptomatology in six patients who had not previously responded to a neuroleptic.

These studies indicate that SSRIs may be helpful in treatment of non-cognitive features of dementia but are unlikely to improve cognition. Consistent with this view, Olafsson et al[104] in a double-blind placebo-controlled study of fluvoxamine (150 mg/day) in 46 elderly patients with dementia found no difference in cognitive function in either the placebo or active treatment group over the 6 weeks of the study. The only difference between groups was a trend favoring those on fluvoxamine with regard to confusion, irritability, anxiety, depression etc., but this did not reach significance. Nordberg[105] in a review of pharmacological treatments for cognitive dysfunction suggests that the SSRIs may be complementary to drugs with more specific effects on cognition but found no evidence for direct actions to improve cognition.

Behavioral Disturbances in Dementia

Open trials of SSRI treatment of behavioral disturbance in dementia where there is no coexisting mood disturbance have been reported. Trappler and Vinuela[106] described the treatment of three patients with dementia (two SDAT, one multi-infarct) and stereotyped behaviors with fluvoxamine at a maximum dose of 150 mg/day. In two patients, complete resolution of these behaviors occurred within 6 weeks, the other patient had some residual symptoms but an overall noticeable improvement after 8 weeks. Pollock et al[107] conducted an open trial of citalopram in 16 patients with dementia and associated behavioral distur-

bance, finding that 13 of the patients tolerated the medication of whom 9 had a "clinically impressive response." A statistically significant overall reduction in shouting and calling out was observed.

Tolerability

Within all patient groups, and particularly in the elderly, careful consideration has to be given to the frequency and severity of adverse events of medication. Some have argued that relative lack of cardiotoxicity and anticholinergic side-effects make SSRIs a preferred choice when compared with tricyclic antidepressants.[94,108] Specifically, Fisch[109] found that fluoxetine, unlike imipramine, amitriptyline and doxepin, caused no changes in the ECG. Finkel,[110] in a review of the literature on the treatment of depression in the over-70s, notes a paucity of research in this population although he states that the literature suggests similar efficacy but increased tolerability for SSRIs compared with tricyclic antidepressants. One area of particular concern in the elderly is possible detrimental effects on cognition. Oxman's review[111] concluded that cognitive impairment as a result of antidepressant treatment was more rare with SSRIs than tricyclics. Unlike other authors, however, he stated that there was some evidence that the SSRIs may actually improve cognition by methods other than just their antidepressant effects. Kerr et al[112] examined psychomotor performance in normal male volunteers over the age of 60 given paroxetine (20 mg/day) as single or repeated doses, and acute doses of lorazepam (1 mg) with and without alcohol (0.6 g/kg of body weight). Paroxetine was shown not to affect performance in any group.

Delirium occurring due to SSRI use was reported by Amir, Dano and Joffe[113] in a 71 year-old female with Type 2 bipolar affective disorder and an old lacunar brain infarct, although the patient was on other medication (trazodone). A history of a previous episode of transient agitated confusion was obtained following treatment with fluvoxamine, alprazolam and brotazolam. Both episodes resolved on withdrawal of treatment. A specific complication of SSRI use is the 5-HT (serotonin) syndrome. Ebert et al[114] prospectively studied 200 inpatients treated with fluvoxamine, over 8200 treatment days, for the occurrence of the 5-HT syndrome. They also included retrospective follow-up data of out-patient treatment covering a further 8891 treatment days. No 'full-blown' 5-HT syndrome occurred but three patients developed reversible changes of mental state with insomnia, agitation, confusion and incoherent thoughts. They estimated that the occurrence of such symptoms, due to serotonergic stimulation, was between 0.006 and 0.04 per 100 treatment days and that the 5-HT syndrome itself was rare.

The peripheral role of 5-HT affecting the gastrointestinal tract is well recognized in all patient groups of whatever age. In elderly patients with depression, and treated with fluoxetine, nortriptyline, desipramine or no medication, Brymer and Winograd[115] noted that those on fluoxetine experienced significantly greater weight loss and were more likely to report nausea and anorexia than the other groups. The weight loss was greatest in those over the age of 75.

Falls in the elderly are a significant cause of morbidity. Mendelson[116] studied the correlation between falls and use of hypnotics and sertraline. It was found that oral benzodiazepines were positively and significantly correlated with falls and that the fall rate for sertraline was the same as the highest rate for benzodiazepines. It was stressed that these were associations and causality could not be implied with any certainty. However Cherin et al[117] in a multi-center case-control study found that fluoxetine was one of only four drugs significantly associated with an increased risk of syncope in the elderly.

One particular group of disorders associated with falls are movement disorders. Exacerbation, or the development, of these could conceivably increase the incidence of falls but Caley and Friedman,[118] in a retrospective study of depressed patients with Parkinson's

disease treated with fluoxetine (40 mg/day), found no evidence that this dose was associated with an increase in the symptomatology of Parkinson's disease. Leo[119] reviewed case reports of movement disorders associated with SSRIs. Seventy-one cases were reported in the literature of which 45.1% had akathisia; 28.2% dystonia; 14.1% parkinsonism and 11.3% tardive dyskinesia-like states. Those affected were more likely to be female and patients suffering from dystonia, parkinsonism or tardive dyskinesia were more likely to be older than those with akathisia. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has been reported in the literature. Burke and Fanker[120] described three new cases of SIADH occurring in elderly patients within one month of commencing fluoxetine for the treatment of depression. All three were treated by withdrawal of fluoxetine and fluid restriction and recovered completely.

The specific issue of treating depressed patients with renal failure was addressed by Levy et al.[121] Nine depressed patients with normal kidney function and seven depressed patients with renal failure undergoing haemodialysis were treated with open-label fluoxetine (20 mg/day) in an 8-week study designed to evaluate the pharmacokinetics of fluoxetine in this population. An equal number of patients in each group completed the study and 83% in each group experienced moderate to marked improvement in their depression. No significant differences in side-effects were observed between groups and those that did occur were minor. The pharmacokinetic data suggested that renal failure and the process of hemodialysis did not significantly alter the pharmacokinetics of fluoxetine or its major metabolite norfluoxetine. Bergstrom et al[122] looked at the effects of renal and hepatic disease on the pharmacokinetics, renal tolerance and risk-benefit profile of fluoxetine. They found comparable results to Levy et al[121] in a similar population undergoing hemodialysis but found that cirrhosis of the liver significantly reduces the clearance of fluoxetine and norfluoxetine.

Cost-Effectiveness of SSRIs

Although treatment with SSRIs is, at face value, more expensive than with the older tricyclic antidepressants there is currently a vigorous debate as to whether overall costs to health and other services differ between treatments. Lapierre et al[123] attempted a cost-effectiveness analysis of paroxetine versus imipramine. They concluded that where continuation rates for paroxetine were greater or equal to 47% it was a more cost-effective treatment than imipramine in the one-year management of patients with moderate to severe depression and that clinical trials report continuation rates of 41-65%. Hotopf, Lewis and Normand[124] looked at both efficacy and cost-effectiveness of SSRIs in comparison with tricyclic antidepressants. Reviewing 105 trials they noted methodological problems that made direct comparisons difficult. They agreed with the generally held view from the trials that SSRIs are as effective as tricyclic antidepressants but slightly fewer patients drop out due to side-effects. They concluded that the cost-effectiveness of SSRIs has not been established. In addition they argued that evaluating the economic aspects of suicide appears impossible because of its 'rarity.' Henry[125] disagreed, quoting his own estimate[126] that the number of antidepressant-related suicides is around 300 per annum, or 50% of all suicides prescribed antidepressants. He further highlighted that most deaths from over-dosage with antidepressants are due to tricyclic antidepressants, with over 80% being due to amitriptyline or dothiepin[127] (see also: Chapter 7). Jonsson and Bebbington[128] attempted to evaluate the cost-effectiveness of the antidepressants, imipramine and paroxetine, by developing a simulation model based on the theory of clinical decision analysis. They estimated the total cost of depressive illness in the UK to be £222 million per annum with expected costs per patient similar for both paroxetine and imipramine. Using this model the cost per successfully treated patient was lower for paroxetine. However, O'Brien[129] pointed out some problems with such simple models, in particular that the assumption that all dropouts (whether from

side-effects or treatment ineffectiveness) carry the same cost is over-simplistic. In addition, the cost of maintenance therapy with antidepressants cannot be judged in the same light as treatment of an acute episode, as variables that support the use of SSRIs (e.g., dropout due to side-effects) are not liable to be an issue in cases of prolonged usage. Further criticism of the Jonsson and Bebbington paper came from Woods and Rizzo[130] who attempted to replicate the work with revised assumptions which, they felt, reflected more clinically relevant treatment patterns. They found that revisions in assumptions about switched-treatment success rates, treatment length and initial treatment success showed that tricyclic antidepressants were equally or more cost-effective than the SSRIs. They therefore argued for use of tricyclic antidepressants as first-choice antidepressant treatment, with SSRIs reserved for those patients not doing well initially. In addition they highlight the problem of establishing valid simulation models and the need for large prospective random-assignment cost-effectiveness studies.

Simon et al[131] attempted to compare clinical, functional and economic outcomes of initial prescription of fluoxetine with outcomes of prescribing imipramine or desipramine in 536 depressed adults commencing antidepressant treatment. Clinical outcomes in all three groups were similar and total health-care costs over 6 months were approximately equal. Higher antidepressant costs for fluoxetine were balanced by lower outpatient visit and inpatient costs. In the elderly Hughes, Morris and McGuire[132] reviewed the effects of drug therapy on the cost of depression. They highlighted that there were no economic studies which examined the cost-effectiveness of antidepressants in this group. They extrapolated from data which suggested that the increased tolerability of SSRIs in the general population makes them more cost-effective but questioned whether this can be applied to the elderly. Their final conclusion was that studies of the economic effects of drug treatments in the elderly need to be carried out.

In summary, the analysis of cost-effectiveness of SSRIs is in its infancy and bedevilled with methodological difficulties. It is, however, clear that it is not possible to conclude that one treatment costs more because the medication is more expensive. Many other factors such as tolerability, compliance, efficacy and the costs of treatment failure need to be considered. It remains unclear[108] as to whether SSRIs are more or less cost-effective than tricyclic antidepressants but Prozac's (fluoxetine) loss of patent protection and availability of cheaper generic versions is likely to change the cost-benefit equation.

References

1. Healey D et al. Child and learning disability psychopharmacology. J Psychopharmacol 1997; 11:291-294
2. Kaplan CA, Hussain S. Use of drugs in child and adolescent psychiatry. Br J Psychiatry 1995; 166:291-298.
3. Barltrop D, Brueton MJ. Paediatric Therapeutics: Principles and Practice, 1991 Butterworth-Heinemann Ltd., Oxford.
4. Rylance G. Drugs for Children. Copenhagen: W.H.O. Regional Office for Europe, 1987.
5. Bahnsen P, Jacobsen E, Thesleff H. The subjective effects of betaphenylisopropylamine-sulfate on normal adults. Acta Med Scand 1938; 97:89.
6. Cameron JS, Specht PG, Wendt GR. Effects of amphetamine on moods, emotions and motivation. J Psychol 1965; 61:93.
7. Riddle MA, Hardin MT, King R et al. Fluoxetine treatment of children and adolescents with Tourette's and obsessive compulsive disorders: Preliminary clinical experience. J Amer Acad Child Adolesc Psychiatry 1990; 29:45-48.
8. Riddle MA, Scahill L, King RA et al. Double-blind, crossover trial of fluoxetine and placebo in children and adolescents with obsessive-compulsive disorder. J Amer Acad Child Adolesc Psychiatry 1992; 31:1062-1069.

9. Anonymous. Fluvoxamine for Childhood OCD. Med Sci Bull 1997; 238:6-7.
10. Apter A, Ratzoni G, King RA et al. Fluvoxamine open-label treatment of adolescent inpatients with obsessive-compulsive disorder or depression. J Amer Acad Child Adolesc Psychiatry 1994; 33:342-348.
11. Geller DA, Biederman J, Reed ED et al. Similarities in response to fluoxetine in the treatment of children and adolescents with obsessive-compulsive disorder. J Amer Acad Child Adolesc Psychiatry 1995; 34:36-44.
12. Liebowitz MR, Hollander E, Schneier F et al. Reversible and irreversible monoamine oxidase inhibitors in other psychiatric disorders. Acta Psychiatrica Scand Suppl. 1990; 360:29-34.
13. Simeon JG, Thatte S, Wiggins D. Treatment of adolescent obsessive-compulsive disorder with a clomipramine-fluoxetine combination. Psychopharmacol Bull 1990; 26:285-290.
14. Alessi N, Bos T. Buspirone augmentation of fluoxetine in a depressed child with obsessive-compulsive disorder. Amer J Psychiatry 1991; 148:1605-1606.
15. Simeon JG, Dinicola VF, Ferguson HB et al. Adolescent depression: A placebo-controlled fluoxetine treatment study and follow-up. Prog Neuro-Psychopharmacol Biol Psychiatry 1990; 14:791-795.
16. Colle LM, Belair JF, DiFeo M et al. Extended open-label fluoxetine treatment of adolescents with major depression. J Child Adolesc Psychopharmacol 1994; 4:225-232.
17. Rodriguez-Ramos P, de Dios-Vega JL, San Sebastian Cabases J et al. Effects of paroxetine in depressed adolescents. Eur J Clin Res 1996; 8:49-61.
18. Jain U, Birmaher B, Garcia M et al. Fluoxetine in children and adolescents with mood disorders: A chart review of efficacy and adverse events. J Child Adolesc Psychopharmacol 1992; 2:259-265.
19. Boulos C, Kutcher S, Gardner D et al. An open naturalistic trial of fluoxetine in adolescents and young adults with treatment-resistant major depression. J Child Adolesc Psychopharmacol 1992; 2:103-111.
20. Kurlan R, Como PG, Deeley C et al. A pilot controlled study of fluoxetine for obsessive-compulsive symptoms in children with Tourette's syndrome. Clin Neuropharmacol 1993; 16:167-172.
21. Como PG, Kurlan R. An open-label trial of fluoxetine for obsessive-compulsive disorder in Gilles de la Tourette's syndrome. Neurology 1991; 41:872-874.
22. Eapen V, Trimble MR, Robertson MM. The use of fluoxetine in Gilles de la Tourette syndrome and obsessive compulsive behaviours: Preliminary clinical experience. Prog Neuro-Psychopharmacol Biol Psychiatry 1996; 20:737-743.
23. Buckingham D, Gaffney G. New TS treatment. J Amer Acad Child Adolesc Psychiatry 1993; 32:224.
24. Cook EH, Jr., Rowlett R, Jaselskis C et al. Fluoxetine treatment of children and adults with autistic disorder and mental retardation. J Amer Acad Child Adolesc Psychiatry 1992; 31:739-745.
25. Ghaziuddin M, Tsai L, Ghaziuddin N. Fluoxetine in autism with depression. J Amer Child Adolesc Psychiatry 1991; 30:508-509.
26. Todd RD. Fluoxetine in autism. Amer J Psychiatry 1991; 148:1089.
27. Mehlinger R, Scheftner WA, Poznanski E. Fluoxetine and autism. J Amer Acad Child Adolesc Psychiatry 1990; 29:985.
28. McDougle CJ, Price LH, Goodman WK. Fluvoxamine treatment of coincident autistic disorder and obsessive-compulsive disorder: A case report. J Autism Devel Disord 1990; 20:537-543.
29. Zametkin AJ, Rapoport JL. Neurobiology of attention deficit disorder with hyperactivity: Where have we come in 50 years? J Amer Acad Child Adolesc Psychiatry 1987; 26:676-686.
30. Adams S. Prescribing of psychotropic drugs to children and adolescents. Br Med J 1991; 302:217.
31. Safer DJ, & Krager JM. A survey of medication treatment for hyperactive/inattentive students. Amer Med Ass 1988; 60:2256-2258.

32. Barrickman L, Noyes R, Kuperman S et al. Treatment of ADHD with fluoxetine: A preliminary trial. J Amer Acad Child Adolesc Psychiatry 1991; 30:762-767.
33. Gammon GD. Fluoxetine and methylphenidate in combination for treatment of attention deficit disorder and comorbid depressive disorder. J Child Adolesc Psychopharmacol 1993; 3:3-10.
34. Pope HG Jr., Hudson JI. Antidepressant medication in the treatment of bulimia nervosa. Psychopathology 1987; 20(Suppl 1):123-129.
35. Jimerson DC, Lesem MD, Hegg AP et al. Serotonin in human eating disorders. Ann NY Acad Sci 1990; 600:532-544.
36. Freeman CP, Hampson M. Fluoxetine as a treatment for bulimia nervosa. Int J Obesity 1987; 11(Suppl 3):171-177.
37. Anonymous. Fluoxetine in the treatment of bulimia nervosa. A multi-centre, placebo-controlled, double-blind trial. Fluoxetine Bulimia Nervosa Collaborative Study Group. Arch Gen Psychiatry 1992; 49:139-147.
38. Goldstein DJ, Wilson MG, Thompson VL et al. Long-term fluoxetine treatment of bulimia nervosa. Fluoxetine Bulimia Nervosa Research Group. Br J Psychiatry 1995; 166:660-666.
39. Robert JM, Lydiard RB. Sertraline in the treatment of bulimia nervosa. Amer J Psychiatry 1993; 150:1753.
40. Ayuso-Gutierrez JL, Palazon M, Ayuso-Mateos JL. Open trial of fluvoxamine in the treatment of bulimia nervosa. Int J Eating Disord 1994; 15:245-249.
41. Brambilla F, Draisci A, Peirone A et al. Combined cognitive-behavioural, psycho-pharmacological and nutritional therapy in bulimia nervosa. Neuropsychobiol 1995; 32:68-71.
42. Mitchell JE, Raymond N, Specker S. A review of the controlled trials of pharmacotherapy and psychotherapy in the treatment of bulimia nervosa. Int J Eating Disord 1993; 14:229-247.
43. Boyer WP & Feighner JP. Antidepressant dose-response relationship in Bulimia. Presented at the XIX CINP Meeting 1994; Washington DC.
44. Russell J, Beumont P, Touyz S et al. Fluoxetine and the management of Bulimia Nervosa. Presented at the XIX CINP Meeting 1994; Washington DC.
45. Herzog DB, Sacks NR. Bulimia nervosa: Comparison of treatment responders vs. non-responders. Psychopharmacol Bull 1993; 29:121-125.
46. Antelman S, Rowland N, Kocan D. Anoretics: Lack of cross tolerance among serotonergic drugs and sensitisation of amphetamine's effect. In: Garattini S and Samanin, R., eds. Anoretic Agents: Mechanism of Action and Tolerance. New York, Raven Press, 1981:4561.
47. Ferguson JM. Treatment of an anorexia nervosa patient with fluoxetine. Amer J Psychiatry 1987; 144:1239.
48. Gwirtsman HE, Guze BH, Yager J et al. Fluoxetine treatment of anorexia nervosa: An open clinical trial. J Clin Psychiatry 1989; 51:378-382.
49. Kaye WH, Weltzin TE, Hsu LK et al. An open trial of fluoxetine in patients with anorexia nervosa. J Clin Psychiatry 1991; 52:464-471.
50. Johnson SR. The epidemiology and social impact of premenstrual symptoms. Clin Obstetrics and Gynaecology 1987; 30:367-376.
51. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 3rd Edition—Revised. Washington, DC: American Psychiatric Association, 1987.
52. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th Edition. Washington, DC: American Psychiatric Association, 1994.
53. Steiner M, Steinberg S, Stewart D et al. Fluoxetine in the treatment of premenstrual dysphoria. New Eng J Med 1995; 32:1529-1534.
54. van Leusden HA. Premenstrual syndrome no progesterone: Premenstrual dysphoric disorder no serotonin deficiency. Lancet 1995; 346:1443-1444.
55. Stone AB, Pearlstein TB, Brown WA. Fluoxetine in the treatment of premenstrual syndrome. Psychopharmacol Bull 1990; 26:331-335.
56. Stone AB, Pearlstein TB, Brown WA. Fluoxetine in the treatment of late luteal phase dysphoric disorder. J Clin Psychiatry 1991; 52:290-293.

57. Wood SH, Mortola JF, Chan YF et al. Treatment of premenstrual syndrome with fluoxetine: A double-blind, placebo-controlled, crossover study. Obstetrics & Gynaecology 1992; 80:339-344.
58. Su TP, Schmidt PJ, Danaceau MA et al. Fluoxetine in the treatment of Premenstrual Dysphoria. Neuropsychopharmacology 1997; 16:346-356.
59. Menkes DB, Taghavi E, Mason PA et al. Fluoxetine's spectrum of action in premenstrual syndrome. Int Clin Psychopharmacol 1993; 8:95-102.
60. Pearlstein TB, Stone AB. Long-term fluoxetine treatment of late luteal phase dysphoric disorder. J Clin Psychiatry 1994; 55:332-335.
61. Steiner M, Steinberg S, D. S. Fluoxetine in the treatment of Premenstrual Dysphoria. New Eng J Med 1995; 332:1529-1534.
62. Elks ML. Open trial of Fluoxetine therapy for premenstrual syndrome. Southern Med J 1993; 86:503-507.
63. Yonkers KA, Halbreich U, Freeman E et al. Symptomatic improvement of Premenstrual Dysphoric Disorder with sertraline treatment. J Amer Med Ass 1997; 278:983-988.
64. Eriksson E, Hedberg MA, Andersch B et al. The serotonin reuptake inhibitor paroxetine is superior to the noradrenaline reuptake inhibitor maprotiline in the treatment of premenstrual syndrome. Neuropsychopharmacology 1995; 12:167-176.
65. Mehlman PT, Higley JD, Faucher I et al. Low CSF 5-HIAA concentrations and severe aggression and impaired impulse control in non-human primates. Am J Psychiatry 1994; 151:1485-1491.
66. Higley JD, Mehlman PT, Poland RE et al. CSF testosterone and 5-HIAA correlate with different types of aggressive behaviours. Biol Psychiatry 1996; 40:1067-1082.
67. Coccaro EF. Central serotonin and impulsive aggression. Br J Psychiatry; 155(Suppl 1989): 52-62.
68. O'Keane V, Moloney E, O'Neill H et al. Blunted prolactin responses to d-fenfluramine in sociopathy. Evidence for subsensitivity of central serotonergic function. Br J Psychiatry 1992; 160:643-646.
69. Coccaro EF, Kavoussi RJ, Sheline YI et al. Impulsive aggression in personality disorder correlates with tritiated paroxetine binding in the platelet. Arch Gen Psychiatry 1996; 53:531-536.
70. Coccaro EF, Kavoussi RJ, Hauger RL. Serotonin function and anti-aggressive response to fluoxetine: A pilot study. Biol Psychiatry 1997; 42:546-552.
71. Coccaro EF, Astill JL. Central serotonergic function in parasuicide. Prog Neuro-Psychopharmacol Biol Psychiatry 1990; 14:663-674.
72. Coccaro EF, Astill JL, Herbert JL et al. Fluoxetine treatment of impulsive aggression in DSM-III-R personality disorder patients. J Clin Psychopharmacol 1990; 10:373-375.
73. Kavoussi RJ, Liu J, Coccaro EF. An open trial of sertraline in personality disordered patients with impulsive aggression. J Clin Psychiatry 1994; 55:137-141.
74. Salzman C, Wolfson AN, Schatzberg A et al. Effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. J Clin Psychopharmacol 1995; 15:23-29.
75. Fava M, Rosenbaum JF, McCarthy M et al. Anger attacks in depressed outpatients and their response to fluoxetine. Psychopharmacol Bull 1991; 27:275-279.
76. Fava M, Rosenbaum JF, Pava JA et al. Anger attacks in unipolar depression, Part 1: Clinical correlates and response to fluoxetine treatment. Am J Psychiatry 1993; 150:1158-1163.
77. Fava M, Alpert J, Nierenberg AA et al. Fluoxetine treatment of anger attacks: A replication study. Annals Clin Psychiatry 1996; 8:7-10.
78. Robinson RG, Parikh RM, Lipsey JR et al. Pathological laughing and crying following stroke: validation of a measurement scale and a double-blind treatment study. Am J Psychiatry 1993; 150:186-293.
79. Andersen G, Vestergaard K, Riis JO. Citalopram for post-stroke pathological crying. Lancet 1993; 342:837-839.
80. Mukand J, Kaplan M, Senno RG et al. Pathological crying and laughing: Treatment with sertraline. Arch Physical Med Rehab 1996; 77:1309-1311.

81. Sloan RL, Brown KW, Pentland B. Fluoxetine as a treatment for emotional lability after brain injury. Brain Injury 1992; 6:315-319.
82. Seliger GM, Hornstein A, Flax J et al. Fluoxetine improves emotional incontinence. Brain Injury 1992; 6:267-270.
83. Preskorn HS. Recent pharmacologic advances in antidepressant therapy for the elderly. Am J Med 1993; 94(Suppl 5A):2-12.
84. Gottfries CG, Karlsson I, Nyth AL. Treatment of depression in elderly patients with and without dementia disorders. Int Clin Psychopharmacol 1992; 6(Suppl 5):55-64.
85. Gottfries CG. Scandinavian experience with citalopram in the elderly. Int Clin Psychopharmacol 1996; 11(Suppl 1):41-44.
86. Tollefson GD, Bosomworth JC, Heiligenstein JH et al. A double-blind, placebo-controlled clinical trial of fluoxetine in geriatric patients with major depression. The Fluoxetine Collaborative Study Group. Int Psychogeriatrics 1995; 7:89-104.
87. Altamura AC, De Novellis F, Guercetti G et al. Fluoxetine compared with amitriptyline in elderly depression: A controlled clinical trial. Int J Clin Pharmacol Res 1989; 9:391-396.
88. Cohn CK, Shrivastava R, Mendels J et al. Double-blind, multi-centre comparison of sertraline and amitriptyline in elderly depressed patients. J Clin Psychiatry 1990; 51(Suppl B):28-33.
89. Hutchinson DR, Tong S, Moon CA et al. Paroxetine in the treatment of elderly depressed patients in general practice: A double-blind comparison with amitriptyline. Int Clin Psychopharmacol 1992; 6(Suppl 4):43-51.
90. Stuppaeck CH, Geretsegger C, Whitworth AB et al. A multi-centre double-blind trial of paroxetine versus amitriptyline in depressed inpatients. J Clin Psychopharmacol 1994; 14:241-246.
91. Geretsegger C, Bohmer F, Ludwig M. Paroxetine in the elderly depressed patient: Randomised comparison with fluoxetine of efficacy, cognitive and behavioural effects. Int Clin Psychopharmacol 1994; 9:25-29.
92. Dunbar GC. Paroxetine in the elderly: A comparative meta-analysis against standard antidepressant pharmacotherapy. Pharmacology 1995; 51:137-144.
93. Schneider LS, Olin JT. Efficacy of acute treatment for geriatric depression. Int Psychogeriatrics 1995; 7(Suppl):7-25.
94. Menting JE, Honig A, Verhey FR et al. Selective serotonin reuptake inhibitors (SSRIs) in the treatment of elderly depressed patients: A qualitative analysis of the literature on their efficacy and side-effects. Int Clin Psychopharmacol 1996; 11:165-175.
95. Small GW, Hamilton SH, Bystritsky A et al. Clinical response predictors in a double-blind, placebo-controlled trial of fluoxetine for geriatric major depression. Fluoxetine Collaborative Study Group. Int Psychogeriatrics 1995; (Suppl):41-53.
96. Koran LM, Hamilton SH, Hertzman M et al. Predicting response to fluoxetine in geriatric patients with major depression. J Clin Psychopharmacol 1995; 15:421-427.
97. Devanand DP, Nobler MS, Singer T et al. Is dysthymia a different disorder in the elderly? Am J Psychiatry 1994; 151:1592-1599.
98. Nobler MS, Devanand DP, Kim MK et al. Fluoxetine treatment of dysthymia in the elderly. J Clin Psychiatry 1996; 57:254-256.
99. Taragano FE, Lyketsos CG, Mangone CA et al. A double-blind, randomised, fixed-dose trial of fluoxetine vs. amitriptyline in the treatment of major depression complicating Alzheimer's disease. Psychosomatics 1997; 38:246-252.
100. Nyth AL, Gottfries CG. The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. A Nordic multi-centre study. Br J Psychiatry 1990; 157:894-901.
101. Volicer L, Rheaume Y, Cyr D. Treatment of depression in advanced Alzheimer's disease using sertraline. J Geriatric Psychiatry Neurol 1994; 7:227-229.
102. Ragneskog H, Eriksson S, Karlsson I et al. Long-term treatment of elderly individuals with emotional disturbances: An open study with citalopram. Int Psychogeriatrics 1996; 8:659-668.
103. Burke WJ, Dewan V, Wengel SP et al. The use of selective serotonin reuptake inhibitors for depression and psychosis complicating dementia. Int J Geriatric Psychiatry 1997; 12:519-525.

104. Olafsson K, Jorgensen S, Jensen HV et al. Fluvoxamine in the treatment of demented elderly patients: A double-blind, placebo-controlled study. Acta Psychiatr Scand 992; 5:453-456.
105. Nordberg A. Pharmacological treatment of cognitive dysfunction in dementia disorders. Acta Neurol Scand Suppl. 1996; 168:87-92.
106. Trappler B, Vinuela LM. Fluvoxamine for stereotypic behaviour in patients with dementia. Ann Pharmacother 1997; 31:578-581.
107. Pollock BG, Mulsant BH, Sweet R et al. An open pilot study of citalopram for behavioural disturbances of dementia. Plasma levels and real-time observations. Am J Geriatric Psychiatry 1997; 5:70-78.
108. Skerritt U, Evans R, Montgomery SA. Selective serotonin reuptake inhibitors in older patients. A tolerability perspective. Drugs and Ageing 1997; 10:209-218.
109. Fisch C. Effect of fluoxetine on the electrocardiogram. J Clin Psychiatry 1985; 46:42-44.
110. Finkel SI. Efficacy and tolerability of antidepressant therapy in the old-old. J Clin Psychiatry 1996; 57(Suppl 5):23-28.
111. Oxman TE. Antidepressants and cognitive impairment in the elderly. J Clin Psychiatry 1996; 57(Suppl 5):38-44.
112. Kerr JS, Fairweather DB, Mahendran R et al. The effects of paroxetine, alone and in combination with alcohol on psychomotor performance and cognitive function in the elderly. Int Clin Psychopharmacol 1992; 7:101-108.
113. Amir I, Dano M, Joffe A. Recurrent toxic delirium in a patient treated with SSRIs: Is old age a risk factor? Israel J Psychiatry and Related Sci 1997; 34:119-121.
114. Ebert D, Albert R, May A et al. The serotonin syndrome and psychosis-like side-effects of fluvoxamine clinical use: An estimation of incidence. Eur Neuropsychopharmacol 1997; 7:71-74.
115. Brymer C, Winograd CH. Fluoxetine in elderly patients: Is there cause for concern? J Am Geriatrics Soc 1992; 40:902-905.
116. Mendelson WB. The use of sedative/hypnotic medication and its correlation with falling down in the hospital. Sleep 1996;19:698-701.
117. Cherin P, Colvez A, Deville de Periere G et al. Risk of syncope in the elderly and consumption of drugs: A case-control study. J Clin Epidemiol 1997; 50:313-320.
118. Caley CF, Friedman JH. Does fluoxetine exacerbate Parkinson's disease? J Clin Psychiatry 1992;5 3:278-282.
119. Leo RJ. Movement disorders associated with the serotonin selective reuptake inhibitors. J Clin Psychiatry 1996; 57:449-454.
120. Burke D, Fanker S. Fluoxetine and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Australian and New Zealand J Psychiatry 1996; 30:295-298.
121. Levy NB, Blumenfield M, Beasley CM Jr. et al. Fluoxetine in depressed patients with renal failure and in depressed patients with normal kidney function. Gen Hosp Psychiatry 1996; 18:8-13.
122. Bergstrom RF, Beasley CM, Jr., Levy NB et al. The effects of renal and hepatic disease on the pharmacokinetics, renal tolerance, and risk-benefit profile of fluoxetine. Int Clin Psychopharmacol 1993; 8:261-266.
123. Lapierre Y, Bentkover J, Schainbaum S et al. Direct cost of depression: Analysis of treatment costs of paroxetine versus Imipramine in Canada. Can J Psychiatry—Rev Can de Psychiatrie 1995; 40:370-377.
124. Hotopf M, Lewis G, Normand C. Are SSRIs a cost-effective alternative to tricyclics? Br J Psychiatry 1996; 168:404-409.
125. Henry JA. Suicide and the cost-effectiveness of antidepressants. Br J Psychiatry 1997; 170:88.
126. Henry JA. Suicide risk and antidepressant treatment. J Psychopharmacol 1996; 19:39-40.
127. Henry JA, Alexander CA, Sener EK. Relative mortality from overdose of antidepressants. Br Med J 1995; 310:221-224.
128. Jonsson B, Bebbington PE. What price depression? The cost of depression and the cost-effectiveness of pharmacological treatment. Br J Psychiatry 1994; 164:665-673.
129. O'Brien J. Cost-effectiveness of antidepressants. Br J Psychiatry 1994; 165:411-412.

130. Woods SW, Rizzo JA. Cost-effectiveness of antidepressant treatment reassessed. Br J Psychiatry 1997; 170:257-263.
131. Simon GE, VonKorff M, Heiligenstein JH et al. Initial antidepressant choice in primary care. Effectiveness and cost of fluoxetine vs. tricyclic antidepressants. JAMA 1996; 275:1897-1902.
132. Hughes D, Morris S, McGuire A. The cost of depression in the elderly. Effects of drug therapy. Drugs and Ageing 1997; 10:59-68.

CHAPTER 5

SSRIs, Drug Withdrawal and Abuse: Problem or Treatment?

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Selective serotonin reuptake inhibitors (SSRIs) have considerable advantages over earlier antidepressants, such as most tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), but like all drugs they also have adverse effects. Advantages of SSRIs include: greater tolerability and safety and a wider range of clinical applications, one of which is a potential use in the treatment of drug abuse and some eating disorders (see also: Chapter 4). However, recent evidence shows that SSRIs are associated with a withdrawal reaction on discontinuation after regular use. A further emerging problem is that SSRIs may themselves be entering the repertoire of polydrug abusers. Three aspects of SSRIs are considered in this chapter: withdrawal effects after chronic administration, potential therapeutic value in the treatment of drug abuse and the possibility of SSRI abuse.

The SSRI Withdrawal (Discontinuation) Syndrome

Many, if not all, drugs that cause adaptive receptor changes on chronic administration are liable to be associated with symptoms if the drug is abruptly discontinued. Withdrawal symptoms are well documented for TCAs and related compounds,[1-8] MAOIs,[6] trazodone[9] and the serotonin (5-hydroxytryptamine, 5-HT) noradrenaline reuptake inhibitor (SNRI), venlafaxine,[10] and it is not surprising that similar symptoms can occur on cessation of long-term treatment with SSRIs. The question of whether the emergence of a withdrawal reaction on drug discontinuation is evidence of drug dependence, as defined for therapeutic dose benzodiazepine dependence, is discussed by Medawar.[11]

Withdrawal Symptoms

Reactions following SSRI withdrawal have been reviewed by many authors.[10-16] Symptoms appear 1-10 days after stopping or, occasionally, after reducing the dosage of an SSRI that has been taken regularly for a few months or more; the time of emergence depends on the elimination half-life of the individual drug. The symptoms differ qualitatively from the usual side-effects profile of SSRIs and from the illness for which they were prescribed. They are usually mild, lasting for an average of 10 days, although they can occasionally be severe and sometimes persist for a longer period. They respond rapidly to re-administration of the SSRI concerned and may be avoided or minimized by gradual tapering of dosage.

A characteristic cluster of symptoms, or syndrome, is described in various reports (Table 5.1). Somatic symptoms include: disequilibrium, gastrointestinal symptoms, influenza-like symptoms, sensory disturbances, sleep disturbance and, occasionally, extrapyramidal effects.[17] Psychological symptoms include: anxiety, crying spells, confusion, memory problems, aggression and irritability.

Selective Serotonin Reuptake Inhibitors (SSRIs): Past, Present and Future, edited by S. Clare Stanford. ©1999 R.G. Landes Company.

Table 5.1. Symptoms associated with SSRI withdrawal

Somatic Symptoms	Psychological Symptoms
Disequilibrium dizziness, light-headedness vertigo, ataxia	anxiety, agitation crying spells irritability overactivity
Gastrointestinal anorexia, nausea, vomiting, abdominal cramps	aggression depersonalization decreased concentration confusion
Influenza-like fatigue, lethargy,myalgia chills,sweating, headache, malaise, weakness, palpitations	memory problems lowered mood
Sensory disturbances paresthesia, tremor, sensations of electric shock (often associated with movement)	
Sleep disurbance insomnia, vivid dreams, nightmares	
Extrapyramidal symptoms parkinsonism, akathisia	

Such symptoms have been recorded after withdrawal of all the SSRIs (paroxetine, sertraline, fluoxetine, fluvoxamine and citalopram). The true incidence is not known, but the relative risk appears to be greatest with paroxetine and least with fluoxetine.[12-15,18-20] Price et al[15] analyzed all UK spontaneous adverse drug reaction reports through the 'yellow card' system up to July 1994 and found a 5.1% incidence of withdrawal reactions associated with paroxetine compared with 0.06-0.9% for the other SSRIs. There were 0.3 reports per thousand prescriptions with paroxetine; 0.03 per thousand with sertraline and fluvoxamine and 0.002 with fluoxetine. These proportions agree in general with those reported by Young and Ashton.[18] Both figures are undoubtedly underestimates since they are based on spontaneous reports by doctors, many of whom are unaware of the existence of antidepressant withdrawal symptoms.[21] In small clinical studies involving 6-17 patients, the incidence of withdrawal reactions was 38.5% and 50% for paroxetine[22,23] and 28% for fluvoxamine,[24] while a 34.5% incidence was reported in 55 patients with panic disorder who were withdrawn from paroxetine after 12 weeks of treatment.[25]

Mechanisms

While there is little doubt that withdrawal symptoms can occur when SSRIs are discontinued, their exact mechanisms are far from clear. Several explanations, involving both pharmacodynamic and pharmacokinetic factors, have been suggested to account for the syndrome and for the greater risk associated with paroxetine.[12-14,26] Some symptoms may be at least partially due to cholinergic overactivity resulting from upregulation of

muscarinic receptors which occurs in response to chronic use of SSRIs with anticholinergic effects. Withdrawal of the drug reveals the consequent hyperexcitability of cholinergic systems. Such a mechanism has been proposed for the TCA withdrawal syndrome (which has many features in common with that of SSRIs) and is supported by the observation that TCA withdrawal symptoms have been relieved by anticholinergic agents.[2] In this connection it is relevant that, of all the SSRIs, paroxetine has the greatest affinity for muscarinic receptors in the human brain.[27] Withdrawal symptoms due to cholinergic rebound could include gastrointestinal disturbances, influenza-like symptoms, sleep disturbance and mania. An imbalance between cholinergic and dopaminergic activity might account for the occasional appearance of extrapyramidal symptoms. However, Schatzberg et al[26] consider that cholinergic rebound is likely to be a factor only in paroxetine withdrawal symptoms since the other SSRIs have only minimal anticholinergic effects. Even for paroxetine, this explanation may be incomplete: in two reported cases[28] a withdrawal reaction to paroxetine occurred despite treatment with desipramine which binds to the muscarinic cholinergic receptor with approximately equal affinity.

A second factor proposed to account for SSRI withdrawal effects is a decline in serotonergic transmission, although there is no direct evidence for this and the mechanisms for producing particular withdrawal symptoms are obscure. Chronic administration of SSRIs is believed to cause downregulation or desensitization of inhibitory $5HT_{1A}$-autoreceptors with the result that serotonergic neurotransmission is increased.[29-31] It is hypothesized that following discontinuation of the SSRI this effect is reversed and a relative deficiency of 5-HT in synapses ensues.[26] Decreased serotonergic neurotransmission might account for withdrawal symptoms such as sleep disorder, with rebound of rapid-eye-movement sleep (REMS) and nightmares,[13] impulsive and aggressive behavior and mood changes.[26] Dizziness, vertigo, nausea and paresthesia have also been linked with the role of 5-HT in coordinating sensory and autonomic function with gross motor behavior.[32] The nature of any such link is obscure but some authors[13,26] point out that such symptoms are often provoked by movement. It is further suggested that extrapyramidal withdrawal symptoms may be related to effects on 5-HT-mediated inhibition of dopaminergic neurotransmission.[10] With regard to individual SSRIs, the most selective SSRI is citalopram, followed by paroxetine which is the most potent.[26] The least selective SSRI is fluoxetine which has some dopamine and noradrenaline reuptake blocking effect.[29] Nevertheless SSRIs may have fewer selective effects in vivo than in vitro tests suggest. Sheline et al[33] found that after 6 weeks treatment with fluvoxamine or fluoxetine in depressed patients, cerebrospinal fluid (CSF) concentrations of the monoamine metabolites 5-hydroxyindoleacetic acid (5-HIAA), 3-methoxy-4-hydroxyphenyl glycol (MHPG) and homovanillic acid (HVA) were reduced by 57%, 48% and 17%, respectively. These results indicate that the drugs, perhaps as a secondary action, affected noradrenergic and dopaminergic neurons as well as serotonergic systems.

A third factor of considerable importance in determining SSRI withdrawal effects concerns their pharmacokinetics. There is a large variation in the rate of elimination between different SSRIs (Table 5.2). For example, the plasma elimination half-life of paroxetine on chronic dosage is about 21 h, while that of fluoxetine is several days. Citalopram and fluvoxamine also have relatively short elimination half-lives, while both sertraline and fluoxetine form pharmacologically active metabolites. The demethylated metabolite of fluoxetine, norfluoxetine, has an elimination half-life of 7-15 days which further prolongs the activity of this compound. Norfluoxetine is further metabolized to a number of other compounds, many of which are unidentified.[14,34]

All the SSRIs are metabolized by the P450 enzyme CYP2D6, which itself shows genetic polymorphism resulting in interindividual variation in rates of metabolism (up to 10% of Caucasians are slow metabolizers of SSRIs) (see also: Chapter 2). Furthermore, paroxetine,

Table 5.2. Pharmacokinetic differences between different SSRIs

SSRI	Plasma elimination half-life		Linearity of pharmacokinetics
	single dose	multiple dose [active metabolite]	
Paroxetine	10 h.	21 h.	Nonlinear
Fluvoxamine	11h.	14 h.	Nonlinear
Sertraline	26h.	26 h. [36 h.]	Linear
Citalopram	33 h.	33 h.	Linear
Fluoxetine	1.9 days	5.7 days [7-15 days]	Nonlinear

Nonlinear: elimination half-life longer at higher plasma concentrations, due to autoinhibition of metabolism; Linear: elimination half-life not dependent on plasma concentration (based on Ref. 14)

and fluoxetine at high plasma concentrations inhibit their own metabolism by CYP2D6 such that they display non-linear pharmacokinetics with a longer elimination half-life at high concentrations, but a more rapid elimination rate as plasma concentrations fall.[12,14] In the case of paroxetine, with its already short half-life, the faster elimination rate, as plasma levels fall following drug discontinuation, may bring about a relatively acute state of cholinergic and serotonergic dysregulation, especially as different receptor adaptations to the drug's presence may reverse at different rates. Possibly this rapid change accounts for the increased prevalence of withdrawal reactions. In contrast, the slow elimination of fluoxetine may allow time for intrinsic readjustment of receptor sensitivities and therefore attenuate withdrawal symptoms.

Management of Withdrawal

Although the mechanisms of the withdrawal reaction from SSRIs require further explanation, it is clear from clinical evidence that the symptoms can be minimized or avoided by slow tapering of dosage. The principles are similar to those recommended for benzodiazepine withdrawal.[35] Schatzberg et al[16] suggest that paroxetine should be reduced by 5 mg/week, and tapering of the shorter half-life SSRIs, especially fluvoxamine and paroxetine, may have to continue for several months. The longer elimination half-life of fluoxetine and norfluoxetine to some extent protects against withdrawal symptoms, but nevertheless reactions can occur even from fluoxetine in some patients.[36] If withdrawal symptoms from any of the SSRIs occur, Lejoyeux et al[10] recommend that the dosage of the drug should be temporarily increased and then tapered again at a slower rate. Although it might appear rational, it is not always possible to substitute one SSRI for another: Lane (1996)[13] quotes the case of a patient who apparently developed withdrawal symptoms three days after switching from paroxetine to sertraline.

Certain patients may be especially vulnerable to withdrawal reactions. These may include patients with anxiety or panic disorders,[25] those who have been on high dosage and those who have had a long duration of treatment. Such patients may require frequent consultations during the course of withdrawal.[10] Ironically, the 10% of slow metabolizers of SSRIs, due to deficiency of the cytochrome P450 CYP2D6 enzyme, may be partially protected from a withdrawal reaction.

On a practical level, slow withdrawal of SSRIs may be difficult due to the limited available dosage strength in tablet forms of SSRIs. These may not allow a suitable taper and the use of liquid preparations (available for fluoxetine and paroxetine) may be necessary.

SSRIs in Alcohol and Drug Abuse

Pathways of Reward

It is generally accepted that drugs with addictive properties act on brain systems subserving reinforcement or reward. These mechanisms are exceedingly complex and involve both multiple brain areas and multiple neurotransmitters.

Dopamine Systems

One pathway central to reward is the dopaminergic mesocorticolimbic pathway. This originates from dopamine-containing cell bodies in the ventral tegmental area in the midbrain, passes through the medial forebrain bundle and projects to the nucleus accumbens, olfactory tubercle, frontal cortex and septal area.[37] Many addictive drugs activate this system and it has been claimed that it constitutes the final common pathway for all drugs of abuse.[38] Thus cocaine, amphetamine, opioids, nicotine, alcohol, cannabis and other drugs that are misused have all been shown to increase dopamine release in the nucleus accumbens.[39-41] Natural rewarding behaviors, including sexual activity and food reinforcement, are probably also at least partially mediated by this system.[42] Dopaminergic systems probably underlie the positive motivational or incentive aspects of reward and may form the basis of drug-seeking (approach) behavior.[43]

Opioid Systems

A second, interacting, reward system utilizing endogenous opioids (β-endorphin, enkephalins) appears to form the basis for consummatory rewards.[37,43] Although opioids increase dopamine release in the nucleus accumbens, they also subserve reinforcement in animals by a non-dopaminergic mechanism. For example, lesions of the nucleus accumbens and dopamine receptor antagonists drastically reduce cocaine and amphetamine self-administration in animals but have much less effect on heroin self-administration. The opioid reward system involves not only the nucleus accumbens but also opioid systems in the periaqueductal grey, amygdala, locus coeruleus and elsewhere. It appears to be largely involved in the consummatory rewards of feeding, drinking, sexual and maternal behavior. Not only opioid narcotics but also alcohol[44] and possibly benzodiazepines and cannabis have important actions on this system.

GABA Systems

A third system postulated to be important for the rewarding actions of sedative/hypnotic drugs is mediated by GABA.[37] Alcohol, barbiturates and benzodiazepines have common actions which include euphoria, disinhibition, anxiety reduction, sedation and hypnosis. In addition, all of these drugs produce a release of punished responding in experimental conflict situations, an effect which correlates well with their clinical actions. This anxiolytic property, mediated by enhancement of GABA activity via interaction with $GABA_A$-benzodiazepine

receptors, may be a major component in the rewarding actions and abuse potential of alcohol and other anxiolytic drugs.[45] As well as providing a positive reward, one important factor in their abuse is that they alleviate the anxiety associated with withdrawal from several other drugs of addiction.

Other Neurotransmitter Systems

Many other neurotransmitters are undoubtedly involved in reward systems. These include noradrenaline, which is particularly important in opioid effects on the locus coeruleus,[46] cholecystokinin (CCK; important in signalling satiety),[47] glutamate, neuropeptide Y[41,48] and others, each of which acts on multiple receptor subtypes. The interplay between these complicated systems and those described above remains obscure but may well be different for different drugs and different types of reward.

Interaction of Serotonergic Pathways with Reward Systems

5-HT appears to play a dual role in reward. There is much evidence for an interaction with the mesolimbic dopaminergic pathway (see also: Chapter 10).[49] Both the ventral tegmental area and the nucleus accumbens receive serotonergic projections from the dorsal and median raphé nuclei. Serotonergic activity in the ventral tegmentum appears to be excitatory, resulting in increased dopamine release in the nucleus accumbens. Consistent with this observation, microinfusion of 5-HT into the ventral tegmentum increases responding of rats for a rewarding electrical stimulation of the medial forebrain bundle, suggesting increased activity in the dopaminergic mesocorticolimbic pathway.

Conversely, serotonergic neurons from the raphé nuclei appear to exert an inhibitory effect on dopaminergic neurons in the nucleus accumbens. Thus, lesions of the dorsal and median raphé nuclei in rats increase dopamine turnover in the nucleus accumbens; injection of 5-HT into the nucleus accumbens inhibits the locomotor effects of cocaine and apomorphine, and 5-HT depolarizes nucleus accumbens neurons in vitro while dopamine hyperpolarizes them.

In summary, serotonergic pathways to the dopaminergic mesolimbic system appear to exert opposing effects, causing excitation in the ventral tegmental area and inhibition in the nucleus accumbens.[49] It is not clear whether the outputs from the dorsal and median raphé nuclei subserve separate functions in the reward-punishment spectrum or whether the opposing effects are mediated by different 5-HT receptors.

There appears to be little information on the interactions between opioids and serotonergic systems[46] but benzodiazepines and alcohol are thought to exert their anxiolytic effects at least partly by decreasing serotonergic activity in critical pathways via GABA enhancement.[50]

5-HT in Addictive Behaviors

In view of these contradictory actions on dopaminergic reward pathways, it is not surprising that the part played by 5-HT in addictive behaviors is uncertain. However, there is some evidence for decreased serotonergic activity in alcoholics,[51] bulimics[52] and possibly in opiate and CNS stimulant abusers, although this may be related to depression. It has been suggested that 5-HT deficiency may underlie drug-seeking behavior,[51] that it is involved in craving[53] and that brain serotonergic activity contributes to satiety[47,52] and modulates the reinforcing effect or 'high' produced by other drugs of addiction.[54] Trials with drugs that increase serotonergic activity, especially SSRIs, are described below, but it should be noted that these constitute only one of several pharmacological approaches to the treatment of drug addiction. It may be that the combined use of other drugs such as naltrexone, acamprosate,[55] clonidine, lofexidine and others[56] is more effective in some cases.

Alcohol

Animal Studies

Several SSRIs including zimelidine, norzimelidine and fluoxetine have been shown to decrease alcohol consumption in alcohol-trained rats in a free-choice environment.[57-59] This effect could occur without significant effects on body weight, total fluid intake or intake of sucrose solution.[58] Drugs with major effects on noradrenaline reuptake (amitriptyline, desipramine, doxepin) did not affect alcohol consumption.[57] Similarly, in rats specially bred for alcohol preference, fluoxetine inhibited intragastric self-administration of alcohol. Treatment with the 5-HT precursor, 5-hydroxytryptophan,[51,60,61] and with 5-HT-releasing agents such as *d*-fenfluramine[51] likewise reduced alcohol consumption. The magnitude of these effects varied between different studies but, with SSRIs, was generally of the order of 40-50% reduction, both in alcohol preference over water and in total alcohol consumption.[51] In all these investigations the effects of SSRIs were immediate, occurring on the first day of administration.

Conversely, destruction of central serotonergic neurons with the selective neurotoxins, 5,6- or 5,7-dihydroxytryptamine, was reported to enhance alcohol consumption in a free-choice environment,[62] and low doses of the 5-HT_{1A}-receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)-tetralin (8-OH-DPAT), which inhibits 5-HT release through activation of somatodendritic 5-HT_{1A}-autoreceptors, actively enhanced alcohol consumption in rats in a free-choice situation.[63] Furthermore, genetically alcohol-preferring rats, high alcohol-consuming rats and alcohol-preferring mice appear to have reduced central serotonergic function as evidenced by low levels of 5-HT and its metabolite, 5-HIAA, as well as decreased receptor densities in several brain areas, compared with non-alcohol-preferring and low-alcohol-consuming rodent lines.[45,64]

Although the above evidence seems fairly consistent in suggesting that low serotonergic activity is associated with increased alcohol consumption and high activity with reduced consumption in rodents, there are some inconsistencies. Most of the drug studies have been limited to short-term drug administration (5-7 days). In one longer-term investigation, Gulley et al[64] studied the time-course of the effects of three SSRIs, fluoxetine, sertraline and paroxetine, on operant lever-pressing for self-administration of alcohol in alcohol-preferring male mice. All the drugs produced initial decreases in lever-pressing for alcohol, but this was followed by a return to baseline over the next few days. After 14 days of treatment, increasing the dose of SSRIs was ineffective in reducing alcohol self-administration. After a washout period of several weeks the drugs again initially decreased alcohol self-administration, followed by a rapid return to baseline. The authors concluded that the effects of SSRIs were related to immediate changes in serotonergic function and that tolerance to this effect developed rapidly.

The role of different types of 5-HT receptors in alcohol consumption is not clear. The effects of SSRIs and 8-OH-DPAT suggest that somatodendritic 5-HT_{1A}-receptors are involved. 5-HT_2-receptor antagonists appear to have no effect[51] but 5-HT_3-receptor antagonists, such as ondansetron, have been observed to reduce alcohol consumption in alcohol-trained marmosets and in alcohol-preferring rats.[49,51,65,66]

Human Studies

The results from animal studies led to clinical investigations of the effects of drugs which modify serotonergic function in alcoholism. SSRIs, including zimelidine, citalopram, viqualine and fluoxetine have been shown in controlled studies to decrease alcohol consumption in non-depressed alcoholics and heavy or problem drinkers.[67] The effect was dose-related and appeared to require greater than the effective antidepressant dose. For

example, fluoxetine at 60 mg/day, but not 40 mg/day, reduced alcohol consumption in problem drinkers. Body weight and appetite also decreased during SSRI treatment, but the loss of weight was greater than could be accounted for by reduction in calories from alcohol. The consumption of non-alcoholic drinks increased and total fluid consumption was not reduced.

Most human studies with SSRIs have been short-term (2-4 weeks). Unlike the antidepressant action, the effect on alcohol consumption appears to be immediate. In the 28-day study of Naranjo et al[67] there was no difference in the reduction of alcohol consumption compared with baseline between the first and second 14-day periods of treatment with fluoxetine (60 mg/day). One open, long-term study of 14 alcohol-dependent patients treated for 6 months with zimelidine (200 mg/day) showed a rapid reduction in alcohol intake (within 1 month) with no sign of tolerance over the whole period, but the patients were also receiving psychosocial therapy.[68] In a 3-month controlled study in 108 non-depressed alcoholics,[69] fluvoxamine was found to be superior to placebo in reducing alcohol consumption, with effects apparent at 15 days and remaining significant at 60 and 90 days. Sertraline also appeared to be effective in decreasing alcohol use and improving mood in an open study of 22 depressed alcoholic patients with a history of multiple relapses.[70]

Although these studies showed a statistically significant reduction in alcohol consumption, the effects of SSRIs were modest. In the study of Balldin et al[68] there was no effect on the daily amount of alcohol taken on drinking days, although the number of drinking days per month was reduced from 14 to between 1 and 5 days. In the study of Naranjo et al[67] there was no significant decrease in the number of days of abstinence, but the number of drinks per day was decreased and the total number of drinks per 14-day assessment period was reduced from 115 to 95 drinks, a reduction of 17.3% from the pre-treatment baseline. Overall, studies with SSRIs in alcoholic patients show a reduction in alcohol consumption of only 9-17%.[51]

There is some evidence for reduced serotonergic function in alcoholism. Low concentrations of CSF 5-HIAA and 5-HT,[71-73] decreased whole blood 5-HT concentration,[74] increased platelet 5-HT uptake[75] and increased platelet [^{3}H]imipramine binding[76] have been found in alcoholics whether drinking or abstaining. However, the same abnormalities occur in other conditions, notably depression and impulsive disorders, and in some of the above studies the alcohol-dependent patients also had anxiety and depressed mood.[72-74] Levels of depression were not stated by Daoust et al,[75] while the patients of Patkar[76,77] were described as alcohol-dependent subjects who were "not being treated for depression." Nevertheless, Sellers et al[51] point out that the effects of SSRIs on alcohol consumption in short-term clinical trials are dose-related and independent of their antidepressant action. Patkar et al[77] also reported a strong positive correlation between craving for alcohol and platelet-rich plasma 5-HT concentrations during detoxification in alcoholic subjects although the relationship between brain serotonergic function and plasma levels of 5-HT was not clear.

Other drugs acting on 5-HT receptors which have been investigated in alcoholic subjects include the 5-HT$_{1A}$-receptor partial agonist, buspirone, the 5-HT$_2$-receptor antagonist, ritanserin, and the 5-HT$_3$-receptor antagonist, ondansetron. Buspirone was reported to decrease alcohol craving and Hamilton rating scales for anxiety and depression in alcoholic subjects with anxiety disorders.[73,78] Ritanserin reduced craving, anxiety and depressive symptoms during alcohol withdrawal in five alcohol-dependent patients.[79] Ondansetron (0.25 mg b.d. and 2 mg b.d.) produced a significant reduction in alcohol consumption after 6 weeks of treatment in a placebo-controlled study in alcohol-dependent subjects.[80] The effect was confined to the more moderate drinkers (less than 10 drinks/day) and was more

marked with the lower dose. The magnitude of effect was modest, about 18% reduction in average drinking over 6 weeks, similar to the reduction observed with SSRIs.

On the whole, the efficacy of drugs affecting central serotonergic activity as therapeutic agents for alcohol dependence is disappointing. Using, as evaluation criteria, the percentage of continuously abstinent subjects and/or percentage of abstinent days, Zernig et al[81] concluded in a review of the literature over the past 10 years that citalopram, fluoxetine and buspirone were virtually without effect and that acamprosate and naltrexone were the most effective drugs for non-depressed alcohol-dependent patients.

Other Drugs of Abuse

SSRIs have also been shown in some animal and human studies to decrease consumption of other reinforcing drugs including cocaine, amphetamine and opiates. In rats, drugs which modify serotonergic function, including fluoxetine, reduced cocaine and amphetamine self-administration[82,83] and zimelidine decreased morphine consumption in morphine-addicted animals.[84] Antagonists of 5-HT_3-receptors did not appear to have similar effects.[85,86] Controlled trials in human drug-abusers are few. In open studies of fluoxetine in cocaine-abusing, heroin addicts entering methadone maintenance programs, cocaine intake and reported craving were reduced in patients taking fluoxetine for at least 1 week.[54,87] The effects appeared to be slow in onset, the steepest decline in consumption occurring at 3 weeks, and to require high dosage of fluoxetine (45-120 mg daily); few subjects achieved total abstinence from cocaine. Some patients reported that fluoxetine decreased the quality of the cocaine 'high' and one reported increased rather than decreased craving for cocaine.

Gawin et al[88] carried out a double-blind placebo-controlled study of desipramine and lithium in 72 subjects who abused cocaine only. Desipramine (2.5 mg/day) decreased cocaine craving and consumption, 59% of the subjects remaining abstinent for 3-4 consecutive weeks of the 6-week study period, compared with 25% on lithium and 17% on placebo. Similar effects have been reported in open studies with imipramine and trazodone. Batki et al[89] conducted a 12-week placebo-controlled study of fluoxetine (40 mg/day) in 32 patients with primary crack-cocaine dependence. The mean dropout rate was significantly greater in the placebo group, only 12% remaining in the study for 6 weeks or more, compared with 68% of those receiving fluoxetine. However, there was no difference in cocaine use or craving between the groups over the first 6 weeks. Other studies cited by Batki et al[89] have shown no benefit from fluoxetine in primary cocaine users or in cocaine users on methadone maintenance.

In amphetamine abusers, Polson et al[90] reported that in a small open study of 13 patients given fluoxetine (20 mg/day) for 14 days, five dropped out; four (two of whom were treated longer than 14 days) achieved total abstinence and, in one, there was no change. Seivewright and Carnwath[91] found that fluoxetine (20 mg/day) decreased consumption of amphetamine (17 subjects) and cocaine (13 subjects) in primary stimulant users. The effects appeared to be most marked in the 18 patients with depression.

Maremmani et al,[53] noting that opiate antagonists are generally inadequate in preventing relapse in heroin abusers because of continued craving, compared the effects in heroin addicts of a combination of fluoxetine (dose not stated) and naltrexone (9 patients) with those of naltrexone alone (9 patients). In the group taking the combination of drugs only one relapsed over a 3 month period, while five in the naltrexone group relapsed. The authors comment: "Fluoxetine may therefore reduce craving which is the Achilles heel of this condition."

In general, the evidence indicates that SSRIs may reduce craving in CNS stimulant and opiate abusers, and possibly decrease the drug-related 'high'. However, not all studies have reported benefits and, as with alcohol dependence, the overall effect on consumption and abstinence is modest. It is not clear whether the positive effects are due to an antidepressant

action[91,92] or to a more direct effect on the mechanisms underlying addiction, but relatively high dosage and at least several weeks of treatment appear to be necessary. There may be important differences between different SSRIs: Boyer and Feighner[92] point out that fluvoxamine but not fluoxetine increases plasma concentrations of methadone, an effect which may be relevant for polydrug users on methadone maintenance. Prevalence of depression may also be higher in this group than in primary stimulant users.

Abuse of SSRIs

Despite the moderate value of SSRIs in the treatment of drug addiction, there is increasing evidence that these drugs, like other antidepressants, may themselves be abused. In view of the two-edged, stimulant and suppressant, actions of 5-HT on reward systems, this observation is perhaps not as paradoxical as it may at first seem.

It has been long known that addiction to MAOIs, especially those with amphetamine-like structures, can occur with some patients taking large doses to maintain stimulant and euphoric effects.[93] There were also reports of abuse of amitriptyline in opiate users on methadone maintenance programs. Cohen et al[94] reported that 25% of 346 methadone maintenance patients in New York admitted to taking amitriptyline for the purpose of achieving euphoria. Evidence of dependency was deduced from the persistent efforts of many patients to have their dosage increased, attempts to forge prescriptions, the presence of an illicit market for amitriptyline and the confirmation by urinalysis that patients who had not been prescribed it were taking the drug. Cantor[95] confirmed that the practice was not uncommon among opiate-dependent patients and that an active street market for amitriptyline had existed in New York for many years. The effect of amitriptyline taken in doses of 50 mg to over 150 mg (sometimes up to 20 pills at once) was described as a sedative euphoria and potentiation of methadone effects.

Somewhat later Dorman et al[96] reported misuse of dothiepin among intravenous drug abusers in Dublin: 46% of 83 addicts at a methadone maintenance clinic admitting to misuse of dothiepin in the previous 6 months. Patients described obtaining euphoria and sedation with complex auditory and visual hallucinations which were regarded as pleasant. Dothiepin was taken orally in doses of 150-600 mg/day.

The abuse potential of MAOIs and TCAs may not be related to their effects on 5-HT since they also increase synaptic levels of noradrenaline and to some extent dopamine. They may thus have some actions in common with amphetamine which increases central dopaminergic, noradrenergic and serotonergic activity and releases dopamine from the nucleus accumbens.[41] However there is now evidence that SSRIs are also occasionally abused and that they are entering the teenage 'rave scene'. Singh[97] and Singh and Catalan[98] reported the use of fluoxetine and sertraline amongst people taking 3,4 methylenedioxy-methamphetamine (MDMA, "Ecstasy") at clubs. Users stated that fluoxetine (20 mg) or sertraline (50 mg) taken with or before Ecstasy prolonged the 'high' from 2 to 4 hours and made it easier to 'come down' with no hangover. Singh (personal communication) points out that MDMA is largely metabolized by the cytochrome P450, CYP2D6, which is inhibited by fluoxetine and sertraline, and suggests that SSRIs enhance and prolong the effects of MDMA by decreasing its rate of metabolism. However, CYP2D6 inhibition by these SSRIs occurs at high plasma concentrations which take time and regular usage to build up[14] while recreational users take single, and not very high doses, of SSRIs irregularly. The 'high' obtained from Ecstasy is thought to be due to release of 5-HT from neurons arising in the raphé nuclei,[99,100] an effect which in animals and possibly humans[101] leads eventually to 5-HT depletion. Ironically, SSRIs appear to block this effect in laboratory animals[97] and may protect against MDMA-induced neurotoxicity. It is not clear whether SSRIs have similar protective effects in humans since they clearly do not inhibit the Ecstasy 'high'.

Abuse of SSRIs is not confined to Ecstasy users. The Alcohol and Drugs Unit in Newcastle-upon-Tyne (personal communication) confirms the not uncommon use of fluoxetine and paroxetine among young people, usually in combination with amphetamines. Users anecdotally say that these drugs (usually 1-3 tablets) enhance and prolong the amphetamine 'high' and that fluoxetine is better than paroxetine for this purpose. Some users also take amitriptyline, using it mainly as a hypnotic. In this connection, it is interesting to note that fluoxetine has been shown to potentiate the stimulant effects of cocaine in rats, suggesting that it could amplify the subjective effects of cocaine in humans.[102]

These observations suggest that misuse of SSRIs may be a hazard for abusers of Ecstasy, lysergic acid diethylamide (LSD), amphetamine and cocaine. To date there appear to have been no reports of SSRI misuse in opiate abusers. It is difficult to calculate the risks, but Zawertailo et al[103] compared the abuse liability of sertraline, alprazolam and *d*-amphetamine in 20 volunteers who were experienced but non-dependent users of CNS depressants and concluded that sertraline had a very low abuse potential compared with the other two drugs. Yet it may be salutary to remember that benzodiazepines were once thought to have a low dependence potential but illicit use of these drugs make them (especially oral and intravenous temazepam) the single most abused category of drug in Scotland.[104]

References

1. Charney DS, Heninger GR, Sternberg DE et al. Abrupt discontinuation of tricyclic antidepressant drugs: Evidence for noradrenergic hyperactivity. Br J Psychiatry 1982; 141:377-386.
2. Dilsaver SC, Kronfol Z, Sackellares JC et al. Antidepressant withdrawal syndromes: Evidence supporting the cholinergic overdrive hypothesis. J Clin Psychopharmacol 1983; 3:157-164.
3. Dilsaver SC, Greden JF, Snider RM. Antidepressant withdrawal syndromes: Phenomenology and physiopathology. Int Clin Psychopharmacol 1987; 2:1-19.
4. Dilsaver SC, Gredon JF. Antidepressant withdrawal phenomena. Biol Psychiatry 1984; 19:237-256.
5. Dilsaver SC. Antidepressant withdrawal syndromes: phenomenology and pathophysiology. Acta Psychiatr Scand 1989; 79:113-117.
6. Tyrer P. Clinical effects of abrupt withdrawal from tricyclic antidepressants and monoamine oxidase inhibitors after long-term treatment. J Affect Disord 1984; 6:1-7.
7. Drug & Therapeutics Bulletin. Problems when withdrawing antidepressives. Drug Ther Bull 1986; 24:29-30.
8. Garner EM, Kelly MW, Thompson DF. Tricyclic antidepressant withdrawal syndrome. Ann Pharmacother 1993; 27:1-68.
9. Otani K, Tanaka O, Kaneko S et al. Mechanisms of the development of trazodone withdrawal symptoms. Int Clin Psychopharmacol 1994; 9:131-133.
10. Lejoyeux M, Adàs J, Mourad I et al. Antidepressant withdrawal syndrome. Recognition, prevention and management. CNS Drugs 1996; 5:278-292.
11. Medawar C The antidepressant Web. Int J Risk & Safety in Med 1997; 10:75-126
12. Lane RM. Withdrawal symptoms after discontinuation of selective serotonin reuptake inhibitors (SSRIs). J Serotonin Res 1986; 3:75-83.
13. Coupland NJ, Bell CJ, Potokar JP. Serotonin reuptake inhibitor withdrawal. J Clin Psychopharmacol. 1996; 16:356-362.
14. Preskorn SH. Clinical pharmacology of selective serotonin reuptake inhibitors. Professional Communications Ltd., Pfizer, USA.
15. Price JS, Waller PC, Wood SM et al. A comparison of the post-marketing safety of four selective serotonin re-uptake inhibitors including the investigation of symptoms occurring on withdrawal. Br J Clin Pharmacol 1996; 42:757-763.
16. Schatzberg AF, Haddad P, Kaplan E et al. Serotonin reuptake inhibitor discontinuation syndrome: A hypothetical definition. J Clin Psychiatry 1997; 58:5-11.

17. Stoukides JA, Stoukides CA. Extrapyramidal symptoms upon discontinuation of fluoxetine. Am J Psychiatry 1991; 148:1263.
18. Young AH, Ashton CH. Pharmacokinetics of fluoxetine. Trends Pharmacol Sci 1996; 17: 400.
19. Young AH, Currie A, Ashton CH. Antidepressant withdrawal syndrome. Br J Psychiatry 1997; 170:288.
20. Committee on Safety of Medicines. Dystonia and withdrawal symptoms with paroxetine (Seroxat). Current Problems in Pharmacovigilance 1993; 19:8.
21. Young AH, Currie A. Physicians' knowledge of antidepressant withdrawal effects: A survey. J Clin Psychiatry 1997; 58:28-31.
22. Keuthen NJ, Cyr P, Ricciardi JA et al. Medication withdrawal symptoms in obsessive-compulsive disorder patients treated with paroxetine. J Clin Psychopharmacol 1994; 14:206-207.
23. Barr LC, Goodman WK, Price LH. Physical symptoms associated with paroxetine discontinuation. Am J Psychiatry 1994; 151:289.
24. Mallya G, White K, Gunderson C. Is there a serotonergic withdrawal syndrome? Biol Psychiatry 1993; 33:851-852.
25. Oehrberg S, Christiansen PE, Behnke K et al. Paroxetine in the treatment of panic disorder. Br J Psychiatry 1995; 167: 374-397.
26. Schatzberg AF, Haddad P, Kaplan E et al. Possible biological mechanisms of the serotonin reuptake inhibitor discontinuation syndrome. J Clin Psychiatry 1997; 58:23-28.
27. Richelson E. The pharmacology of antidepressants at the synapse: Focus on newer compounds. J Clin Psychiatry 1994; 55 (9 Suppl.): 34-39.
28. Fava GA, Grandi S. Withdrawal syndrome after paroxetine and sertraline discontinuation. J Clin Psychopharmacol 1995; 15:374-375.
29. Stanford SC. Prozac: Panacea or puzzle? Trends Pharmacol Sci 1996; 17: 150-154.
30. Goodwin GM. How do antidepressants affect serotonin receptors? Br J Psychiatry 1996; 164:149-152.
31. Deakin JFW. A review of clinical efficacy of 5-HT_{1A} agonists in anxiety and depression. J Psychopharmacol 1993; 7:283-289.
32. Jacobs BL, Fornal CA. 5HT and motor control: A hypothesis. Trends Neurosci. 1993; 16:346-352.
33. Sheline YI, Bardgett ME, Csaernansky JG. Correlated reductions in cerebrospinal fluid 5-HIAA and MHPG concentrations after treatment with selective serotonin reuptake inhibitors. J Clin Psychopharmacol 1997; 17:11-14.
34. Benfield P, Ward A. Fluvoxamine: A review of its pharmacodynamic and therapeutic efficacy in depressive illness. Drugs 1986; 32:313-334.
35. Ashton H. The treatment of benzodiazepine dependence. Addiction 1994; 89: 1535-1541.
36. Berlin CS. Fluoxetine withdrawal symptoms. Br J Addict 1996; 84:547-553.
37. Koob GF. Drugs of abuse: Anatomy, pharmacology and function of reward pathways. Trends Pharmacol Sci 1992; 13:177-84.
38. Wise RA, Bozarth MA. A psychomotor stimulant theory of addiction. Psychol Rev. 1987; 94:469-492.
39. Di Chiara G, Imperator A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci USA 1988; 85:5274-5278.
40. Miller NS, Gold MS. A hypothesis for a common neurochemical basis for alcohol and drug disorders. Recent Adv in Addictive Disord 1993; 16:105-117.
41. Nutt DJ. Addiction: Brain mechanisms and their treatment implications. Lancet 1996; 347:31-36.
42. Philips AG, Fibiger HC. Neuroanatomical bases of intracranial self-stimulation: Untangling the Gordion knot. In: Liebman JM, Cooper SJ, eds. The Neuropharmacologic Basis of Reward. Oxford: Clarendon Press, 1989:66-104.
43. Di Chiara G, North RA. Neurobiology of opiate abuse. Trends Pharmacol Sci 1992; 13:185-193.

44. Herz A. Endogenous opioid systems and alcohol addiction. Psychopharmacology 1997; 129:99-111.
45. Samson HH, Harris RA. Neurobiology of alcohol abuse. Trends Pharmacol Sci 1992; 13:206-211.
46. Simonato M. The neurochemistry of morphine addiction in the neocortex. Trends Pharmacol Sci 1996; 17:410-415.
47. Cooper SJ. 5-HT and ingestive behaviour. In: Marsden CA, Heal DJ, eds. Central Serotonin Receptors and Psychotropic Drugs. London: Blackwell Scientific Publications, 1992: 260-291.
48. Curzon G, Gibson EL, Oluyomi O. Appetite suppression by commonly used drugs depends on 5-HT receptors but not on 5-HT availability. Trends Pharmacol Sci 1997; 18:21-25.
49. Tyers MB, Hayes AG. 5-HT receptors and addiction. In: Marsden CA, Heal DJ, eds. Central Serotonin Receptors and Psychotropic Drugs. London: Blackwell Scientific Publications, 1992: 292-305
50. Gray JA. Anxiety as a paradigm case of emotion. Br Med Bull 1981; 37:193-197.
51. Sellers EM, Higgins GA, Sobell MB. 5-HT and alcohol abuse. Trends Pharmacol Sci 1992; 13:69-75.
52. Kaye WH. Serotonin activity in anorexia and bulimia nervosa. J Psychopharmacol 1992; Meeting of British Association for Psychopharmacology and European Behavioural Pharmacology Society. Abstract 118.
53. Maremmani I, Castrogiovanni P. Daini L et al. Use of fluoxetine in heroin addiction. Br J Psychiatry. 1992; 160:570-571.
54. Batki SL, Manfredi LB, Jacob P et al. Fluoxetine for cocaine dependence in methadone maintenance: Quantitative plasma and urine cocaine/benzoylecgonine concentrations. J Clin Psychophamacol 1993; 13: 243-50.
55. Spanagel R, Zieglgänsberger W. Anti-craving compounds for ethanol: New pharmacological tools to study addictive processes. Trends Pharmacol Sci 1997;18:54-59.
56. Seivewright NA, Greenwood J. What is important in drug misuse treatment? Lancet 1996; 347:373-376.
57. Amit Z, Sutherland EA, Gill K et al. Zimelidine: A review of its effects on ethanol consumption. Neurosci Biobehav Rev 1984; 8:35-54.
58. Rockman GE, Amit Z, Brown W et al. An investigation of the mechanisms of action of 5-hydroxytryptamine in the suppression of ethanol intake. Neuropharmacology 1982; 21:341-347.
59. Murphy JM, Waller MB, Gatto GJ et al. Effects of fluoxetine on the intragastric self-administration of ethanol in the alcohol preferring P line of rats. Alcohol 1988; 5:283-286.
60. Myers RD, Melchior CL. Alcohol and alcoholism: Role of serotonin . In: Essman BW, ed. Serotonin in Health and Disease, Vol. 2. New York: Spectrum, 1977: 373-340.
61. Geller I. Effects of para-chlorphenylalanine and 5-hydroxytryptophan on alcohol intake in the rat. Pharmacol Biochem Behav 1973; 1:361-5.
62. Naranjo CA, Sellers EM, Lawrin MO. Modulation of ethanol intake by serotonin uptake inhibitors. J Clin Psychiatry 1986; 47 (Suppl 4):16-22.
63. Tomkins DM, Higgins GA, Sellers EM. Low doses of the 5-HT_{1A} agonist 8-hydroxy-2-(di-*n*-propylamino)-tetralin (8-OH DPAT) increase ethanol intake. Psychopharmacology 1994; 115:173-9.
64. Gulley JM, McNamar C, Barbera TJ et al. Selective serotonin reuptake inhibitors: Effects of chronic treatment on ethanol-reinforced behavior in mice. Alcohol 1995; 12:177-181.
65. Silvestre JS, Fernandez AG, Palacios JM et al. Effect of 5-HT receptor agonists and antagonists on ethanol intake and preference in rats. J Psychopharmacol.1995; 9(Suppl): Abstract 211.
66. Wilson AW, Neill JC, Costall B. Effect of serotonergic compounds on ethanol preference and food consumption in the rat. Psychopharmacology 1995; 9(Suppl): Abstract 212.
67. Naranjo CA, Kadlec KE, Sanhueza P et al. Fluoxetine differentially alters alcohol intake and other consummatory behaviors in problem drinkers. Clin Pharmacol Ther 1990; 47:490-498.

68. Balldin J, Berggren U, Bokstrom K et al. Six-month open trial with Zimelidine in alcohol-dependent patients: Reduction in days of alcohol intake. Drug Alcohol Depend 1994; 35:245-8.
69. Block BA, Holland RL, Ades J. Recidivist alcoholics: A double-blind placebo-controlled study of fluvoxamine. Neuropsychopharmacology 1994; 10(Suppl 3:2):58-43.
70. O'Brien K. Depression seen during alcohol detoxification: Early intervention with sertraline. Neuropsychopharmacology 1994; 10 No. 3S, Part 2, P-174-5.
71. Ballenger JC, Goodwin FK, Major LF et al. Alcohol and central serotonin metabolism in man. Arch Gen Psychiatry 1979; 36:224-227.
72. Banki CM. Factors influencing monoamine metabolites and tryptophan in patients with alcohol dependence. J Neural Transm 1981; 50:89-101
73. Tollefson GD. Anxiety and alcoholism: A serotonin link. Br J Psychiatry 1991; 159:34-39.
74. Banki CM. 5-Hydroxytryptamine content of the whole blood in psychiatric illness and alcoholism. Acta Psychiatr Scand 1978; 57:232-238.
75. Daoust M, Lhuintre JP, Ernouf D et al. Ethanol intake and 3H-serotonin uptake II: A study in alcoholic patients using platelets 3H-paroxetine binding. Life Sci 1991; 48:1977-1983.
76. Patkar AA, Naik P, Zaman K et al. Plasma serotonin (5-HT) levels and craving in alcohol dependent subjects during withdrawal. J Psychopharmacol. 1994; Joint Meeting of British Association for Psychopharmacology and Interdisciplinary Society for Biological Psychiatry: Abstract 135.
77. Patkar AA, Naik P, Al-Chalabi T et al. Platelet imipramine binding in alcohol dependents. J Psychopharmacol. 1994; Joint Meeting of British Association for Psychopharmacology and Interdisciplinary Society for Biological Psychiatry: Abstract 134.
78. Bruno F. Buspirone in the treatment of alcoholic patients. Psychopharmacology 1989; 22:49-59.
79. Monti JM, Alterwain P. Ritanserin decreases alcohol intake in chronic alcoholics. Lancet 1991; 337:360.
80. Sellers EM, Toneatto T, Romach MK et al. Clinical efficacy of the 5-HT_3 antagonist ondansetron in alcohol abuse and dependence. Alcohol Clin Exp Res. 1994; 18:879-885.
81. Zernig G, Fabisch K, Fabisch H. Pharmacology of alcohol dependence. Trends Pharmacol Sci 1997; 18:229-231,
82. Richardson N, Roberts D. Fluoxetine pretreatment reduces breaking points on a progressive ratio schedule reinforced by intravenous cocaine self-administration in the rat. Life Sci 1991; 49:833-840.
83. Carroll M, Lac S, Asencio M et al. Fluoxetine reduces intravenous cocaine self-administration in rats. Pharmacol Biochem Behav 1990; 35:237-244.
84. Rönnbäck L, Zeuchner J, Rosengren L et al. Decreased morphine intake by opiate addicted rats administered zimelidine, a 5-HT uptake inhibitor. Psychopharmacology 1984; 82:30-35.
85. Joharchi N, Sellers EM, Higgins GA. Effect of 5-HT_3 receptor antagonists on the discriminative stimulus properties of morphine in rats. Psychopharmacology 1993; 112:111-115.
86. Hatcher JP, Boyland P, Hagan JJ. The 5-HT_3 receptor antagonists, granisetron and ondansetron, do not affect cocaine-induced shifts in intra-cranial self-stimulation thresholds. J Psychopharmacol 1995; 9:342-347.
87. Pollack MH, Rosenbaum JF. Fluoxetine treatment of cocaine abuse in heroin addicts. J Clin Psychiatry1991; 52:31-33.
88. Gawin FH, Kleber HD, Byck R et al. Desipramine facilitation of initial cocaine abstinence. Arch Gen Psychiatry 1989; 46:117-121.
89. Batki SL, Washburn AM, Frluvvhi K et al. A controlled trial of fluoxetine in crack cocaine dependence. Drug Alcohol Depend 1996; 41:137-142.
90. Polson RG, Fleming PM, O'Shea JK. Fluoxetine in the treatment of amphetamine dependence. Human Psychopharmacol 1993; 8:55-58.

91. Seivewright N, Carnwath T. Fluoxetine in substance misuse treatment. J Psychopharmacol Joint Meeting of British Association for Psychopharmacology and Interdisciplinary Society for Biological Psychiatry. 1994; Abstract 139.
92. Boyer WF, Feighner JP. Other uses of the selective serotonin re-uptake inhibitors. In: Feighner JP, Boyer WF eds. Selective Serotonin Re-uptake Inhibitors (2nd ed). Chichester: John Wiley & Sons, 1996:267-290.
93. Tyrer PJ. Monoamine oxidase inhibitors and amine precursors. In: Tyrer PJ, ed. Drugs in Psychiatric Practice. London: Butterworth, 1982:249-279.
94. Cohen MJ, Hanbury R, Stimmel B. Abuse of amitriptyline. JAMA 1978; 240:1372-1373.
95. Cantor R. Methadone maintenance and amitriptyline. JAMA 1979; 241:2378.
96. Dorman A, Talbot D, Byrne P et al. Misuse of dothiepin. Br Med J 1995; 11:1502.
97. Singh A. Ecstasy and Prozac. New Scientist 1995; Oct:51.
98. Singh AN, Catalan J. The misuse potential of antidepressants. J Psychopharmacol 1996; 10 (Suppl.): Abstract 122.
99. Barnes DM. (1988) New data intensify the agony over Ecstasy. Science 1988; 239: 864-856.
100. Peroutka SJ. Incidence of recreational use of 3,4-methylenedimethoxymethamphetamine (MDMA, 'Ecstasy') on an undergraduate campus. New Engl J Med 1987; 317:1542-1543.
101. Green AR, Goodwin GM. Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA or 'Ecstasy'). Psychopharmacology 1996; 119:247-260.
102. Cunningham KA, Callahan PM. Monoamine reuptake inhibitors enhance the discriminative state induced by cocaine in the rat. Psychopharmacology 1991; 104:177-178
103. Zawertailo LA, Busto U, Kaplan HL et al. Comparative abuse liability of sertraline, alprazolam, and dextroamphetamine in humans. J Clin Psychopharmacol 1995; 15:117-124.
104. Robertson JR, Ronald PJM. Prescribing benzodiazepines to drug misusers. Lancet 1992; 339:1169-1170.

CHAPTER 6

SSRIs and Sexual Function

Peter A. Sargent and Guy M. Goodwin

Introduction

Human sexual dysfunction is described in ICD-10[1] under broad categories, reflecting the pragmatic division of the normal sexual response, into phases of **desire, arousal, orgasm and resolution:**

F52 Sexual dysfunction, not caused by organic disorder or disease
F52.0 Lack or loss of sexual desire
F52.1 Sexual aversion and lack of sexual enjoyment
F52.2 Failure of genital response
F52.3 Orgasmic dysfunction
F52.4 Premature ejaculation
F52.5 Nonorganic vaginismus
F52.6 Nonorganic dyspareunia
F52.7 Excessive sexual drive
F52.8 Other sexual dysfunction, not caused by organic disorder or disease
F52.9 Unspecified sexual dysfunction, not caused by organic disorder or disease

The pitfalls of medicalizing sexual dysfunction should be noticed here and have been illuminated in the lampoon by Szaz:[2] he has interesting things to say in this area. Accepting the more conventional medical view, nevertheless, epidemiological studies suggest that sexual dysfunction is not uncommon in the general population. An analysis of 22 surveys of psychosexual dysfunction found inhibited sexual desire in 1-15% of men and in 1-35% of women, inhibited sexual excitement in 10-20% of men, premature ejaculation in 35% of men and inhibited orgasm in 5% of men and 5-30% of women.[3] The scale and also the variability of these rates provides a potentially confounding background for the interpretation of findings of sexual dysfunction in specific disorders such as depression or as a consequence of treatment with psychotropic drugs such as the selective serotonin reuptake inhibitors (SSRIs).

The SSRIs are the first among a generation of novel psychotropic drugs with high specificity of primary action. Therefore, in reviewing what is currently understood about their role in producing sexual dysfunction, particular emphasis will be given to the pharmacology of serotonin (5-hydroxytryptamine, 5-HT). This inevitable concentration upon a single neurotransmitter necessarily does scant justice to the role of other neurohumoral systems in the physiology of sexual function.

The Neurobiology of Sexual Function

Sexual desire and arousal have a poorly understood central representation in the brain. Behavioral responses are easier to measure and are known to be determined partly by brain centers directly influencing motor behaviors, and partly by spinal reflexes which can operate

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independently following spinal cord transection. It is axiomatic that reflex responses are usually modified by the stimulatory or inhibitory influence of descending spinal projections and that the underlying neuronal networks provide at least one locus for the variability of sexual function which will underlie clinical problems.

Male Sexual Function

In male rats the medial preoptic area (POA) of the hypothalamus is an important region in the brain controlling sexual behavior. Stimulating the POA produces copulatory behavior.[4] As a functional corollary, there is increased metabolic activity and production of Fos protein (the product of the *c-fos* gene) in the POA during copulation.[5,6] Accordingly, lesioning of the POA impairs male sexual response,[7] but it appears to be explicit responses rather than motivation that are affected.[8] Lesioning the dorsal raphé nucleus and medial forebrain bundle suggests that ascending serotonergic fibers to the POA provide an inhibitory influence to the regulation of male copulatory behavior. Neurons in the POA project to various regions, including dopaminergic neurons in the ventral tegmental area (VTA), where lesions also interfere with male sexual behavior (Fig. 6.1).

The broadly excitatory effects of dopamine and the inhibitory effects of 5-HT will be noticed here. The administration of the dopamine agonist, apomorphine, directly into the POA increases male rat sexual response,[9] whereas dopamine antagonists interfere with this.[10,11] Apomorphine also induces erections in man.[12-17] 5-HT reduces sexual behavior when applied directly to the POA and nucleus accumbens.[18,19] By contrast, when applied directly to the dorsal and median raphé, 5-HT increases sexual response.[20] This augmented sexual response is presumably a consequence of action at inhibitory somatodendritic autoreceptors on serotonergic neurons which will reduce 5-HT release in the terminal fields of these cells. The 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) likewise increases sexual activity when applied directly to the median raphé, where it is a potent agonist at inhibitory somatodendritic autoreceptors.[19]

Testosterone may stimulate male sexual behavior in part by reducing serotonergic neurotransmission. Conversely, castration of male rats increases the level of 5-HT in several hypothalamic areas.[21]

A descending spinal 5-HT pathway, originating in the nucleus paragigantocellularis in the medullary reticular formation, projects to the spinal nucleus of the bulbocavernosum in the ventral horn of the lumbar region of the spinal cord. It appears to exert an inhibitory control on penile erection and penile reflexes because intrathecal administration of 5-HT into the subarachnoid space around the lumbosacral spinal cord reduced penile intromissions, but did not affect mounting behavior.[22-24] Descending serotonergic fibers may act to inhibit sensory transmission from the penis, autonomic output or the firing of motor nuclei mediating erection and ejaculation in male animals.

Erection

Evidence from animal studies and patients with spinal cord injuries suggests that both parasympathetic and sympathetic components may contribute to penile erection. Root[25] demonstrated that if the sacral spinal cord is removed from male cats, they can still develop erections when with a female in estrous, but animals that have had a cord transection above the level of the sympathetic efferent nerves do not show an erectile response. Erection to arousing visual and auditory stimuli is preserved in some of male patients with sacral cord lesions.[26] Patients with damage to the cervical cord can only develop erections following tactile stimulation of the penis, when afferent information is conveyed to the spinal cord via the pudendal nerve. These findings are compatible with a psychogenic pathway via the long thoracic efferent sympathetic fibers of the hypogastric nerve and a reflexogenic pathway via

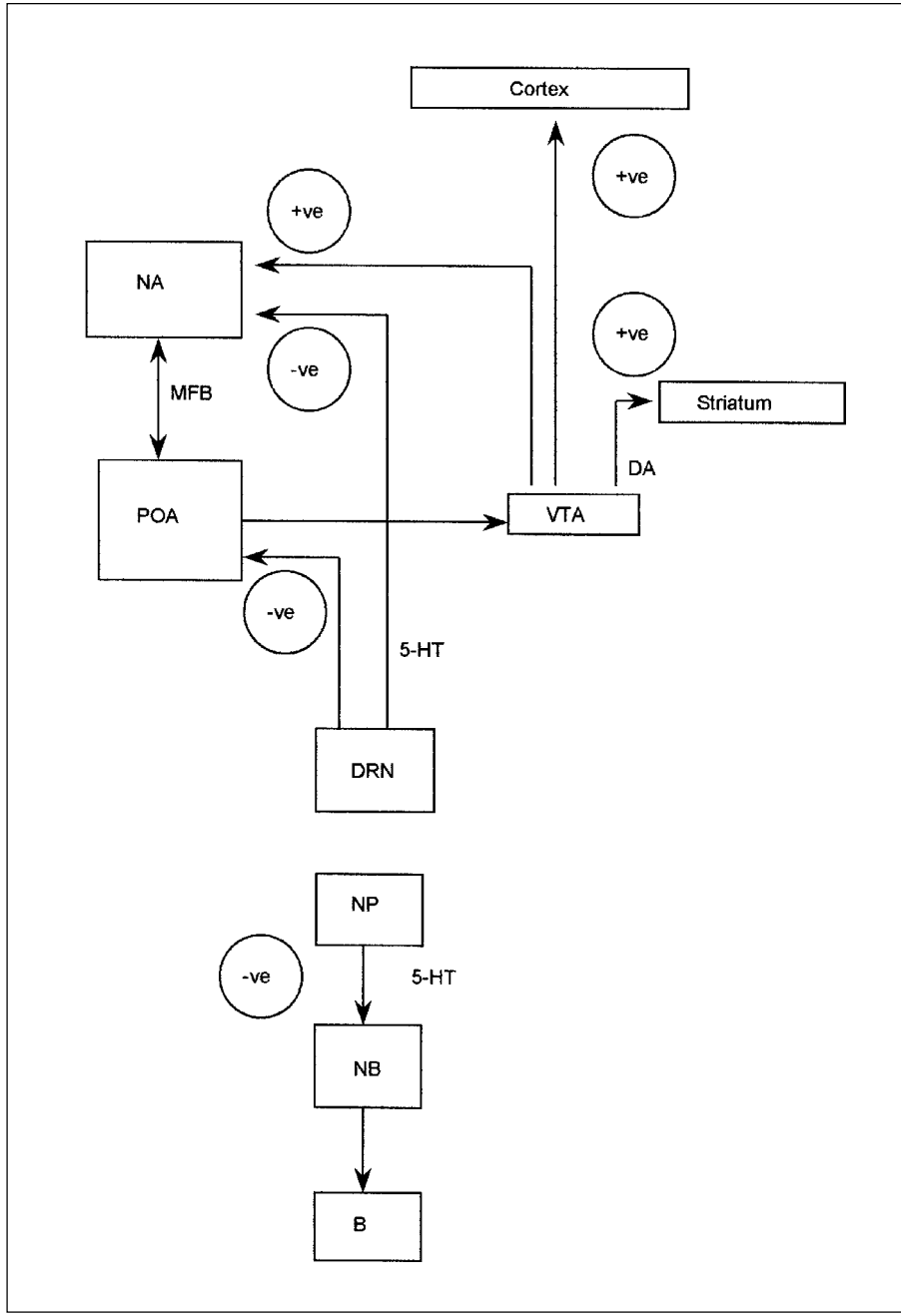

Fig. 6.1. Neural control of male sexual function. +ve, excitatory effects; -ve, inhibitory effects; B, bulbocavernosus; DA, dopamine; DRN, dorsal raphé nucleus; MFB, medial forebrain bundle; NA, nucleus accumbens; NB, nucleus bulbocavernosum; NP, nucleus paragigantocellularis; POA, preoptic area; VTA, ventral tegmental area; 5-HT, 5-hydroxytryptamine.

the efferent parasympathetic fibers from the sacral cord running in the nervi erigentes. Under normal circumstances erection involves pro-erectile neurons located in the sacral parasympathetic nucleus of the L6-S1 spinal cord. Contraction of the ischiocavernosus and bulbospongiosus striated muscles, controlled by motor neurons located in the ventral horn of the L5-L6 spinal cord, reinforces penile erection and contributes to ejaculation (see below).

Male Orgasm

Male orgasm is a two-stage process involving emission (the movement of sperm into the urethra) and ejaculation (the explosive propulsion of the semen out of the urethra). How it is triggered is poorly understood although the inhibitory involvement of 5-HT is increasingly suggested by the pharmacology (described below). Neurons originating in the reticular paragigantocellularis nucleus of the ventral medulla (Fig. 6.1) and projecting to pudendal motor neurons and interneuronal areas of the lumbar cord appear to mediate inhibition of sexual reflexes and the majority of these fibers have been demonstrated to be serotonergic. Emission is a sympathetic response, integrated in the upper lumbar segments of the spinal cord: it involves a sequence of contractions of smooth muscles of the epididymus, vas deferens, seminal vesicles and prostate to expel seminal fluid into the prostatic urethra. Various studies have demonstrated noradrenergic and cholinergic fibers in the epididymus, vas deferens and seminal vesicles. Retrograde ejaculation of seminal fluid into the bladder is prevented by reflex closure of the bladder neck. Motor neurons originating in the spinal nucleus of the bulbocavernosum innervate the skeletal bulbocavernosus muscle in males (and the sphincter vaginae in females). Ejaculation occurs when the seminal fluid is propelled forward by rhythmic contractions of the striated bulbocavernosus and perineal muscles.

The Pharmacology of 5-HT and Male Sexual Function

5-HT Release

It will be clear that the receptor actions of 5-HT are multiple so that, overall, increasing the availability of 5-HT has the potential to produce complex effects: the predominant one is disruption. The effects on ejaculatory latency are particularly consistent in animals. Thus, the 5-HT-releasing agent fenfluramine induces penile erections,[27] but decreases copulatory rate and efficiency, and increases ejaculatory latency in rats.[28] Administration of the 5-HT precursor 5-hydroxytryptophan (5-HTP) in male rats induces penile erections, but also increases the threshold of ejaculation so that a greater number of intromissions occurs before ejaculation and ejaculatory latency is prolonged.[29] Blocking 5-HT synthesis with *p*-chlorophenylalanine (*p*CPA) reduces ejaculatory latency in male rats[30,31] and 5-HT cell destruction by intracerebral injection of 5,7-dihydroxytryptamine (5,7-DHT) increases mating behavior as measured by an increased number of intromissions and ejaculations, and reduced ejaculatory latency and post-ejaculation interval.[32,33] A spinal locus for some of the effects of 5-HT is suggested by its intrathecal infusion into the spinal subarachnoid space at the lumbar level which increased penile intromission latencies[34] and inhibited ejaculation:[35] it has also been observed to abolish the reflex response to urethral stimulation in male rats which normally leads to penile erection, ejaculation and rhythmic contraction of the perineal muscles.[23]

Actions of Drugs at 5-HT_1 Receptors

Systemic administration of 5-HT_{1A} receptor agonists such as 8-OH-DPAT in rats reduces penile erections induced by 5-HT_{2C} agonists[36] and facilitates ejaculation by decreasing ejaculatory threshold and latency (Table 6.1).[37] Administration of 8-OH-DPAT causes a

Table 6.1. Summary of the effects of 5-HT receptor activation in male and female rats

	Receptor	Effect of receptor activation	
Male			
	5-HT_{1A} & 5-HT_{2A}	Reduces erection & increases ejaculation	
	5-HT_{2C}	Increases erection & reduces ejaculation	
Female		Receptive	Non-Receptive
	5-HT_{1A} & 5-HT_{2A}	Inhibits lordosis	stimulates lordosis
	5-HT_{2C}	Stimulates lordosis	Inhibits lordosis

biphasic dose-response pattern in the rhesus monkey. Low doses facilitated ejaculation by reducing ejaculatory threshold and latency, perhaps by a preferential presynaptic action as seen in other models of 5-HT_{1A} receptor function,[38] and high doses interfered with copulation and ejaculation.[39]

Intrathecal administration of lisuride[40] and the more selective 5-HT_{1A} receptor agonist 8-OH-DPAT,[35] however, has a facilitatory effect on male sexual behavior with reduced number of mounts and intromissions before ejaculation, and reduced ejaculation latency.

Actions of Drugs at 5-HT_2 Receptors

Systemic administration of the 5-HT_{2C} receptor agonist, 1-(*m*-chlorophenyl)piperazine, (*m*CCP) induced penile erection[36,41] and delayed ejaculation in male rats and rhesus monkeys[39] (Table 6.1).[31] The potency of 5-HT agonists to induce penile erection corresponds to their affinity for the 5-HT_{2C} receptor.[36] 5-HT_{2C} receptors might modulate the effects of dopaminergic pathways on penile reflexes, as 5-HT antagonists prevent erections caused by dopamine agonists with a potency equivalent to their affinity for the 5-HT_{2C} receptor.[42,43]

After spinal cord transection in rats, administration of the mixed 5-HT_{1A}/5-HT_{2A} receptor agonist 5-methoxy-*N*,*N*-dimethyltrypamine (5-MeODMT) produced a decrease in erectile response and an increase in seminal emission.[44] Furthermore, administration of the 5-HT_{2C} receptor agonist, *m*CPP, in rats was observed to increase penile nerve firing and intracavernous pressure after spinal cord transection.[45] This suggests that 5-HT_{1A} receptor-mediated inhibition of erection and facilitation of ejaculation, and 5-HT_{2C} receptor-mediated facilitation of erection and inhibition of ejaculation, might occur at the spinal level.

Systemic administration of the 5-HT_{2A} receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) also reduces penile erections induced by 5-HT_{2C} agonists at high doses.[36]

Female Sexual Function

Behavioral studies in female rats usually measure sexual receptivity as the lordosis response. The anterior third of the ventromedial nucleus of the hypothalamus (VMN) appears to be the part of the brain which is most important for sexual behavior in the female rat. Electrical stimulation of the VMN in female rats increases female sexual response and female rats with bilateral lesions of the VMN do not show a lordosis response.[46]

Administration of estradiol followed by progesterone activates sexual behavior in female rats. These hormones appear to exert their effects on behavior by activating neurons in the VMN.[47,48] Specifically, the priming effect of estradiol appears to be caused by an increase in the expression of progesterone receptors in the VMN,[49] presumably via genomic effects. Steroid-sensitive neurons of the VMN project to the periaqueductal gray matter (PAG) in the midbrain. Electrical stimulation of the PAG has been found to increase lordosis, while lesions here abolish it.[50,51] Both electrical stimulation of the VMN and estradiol treatment enhanced the rate of neuronal firing in the PAG.[52,53] Lesions that disrupt axons from the VMN projecting to the PAG also prevent the female sexual response.[54] The neurons of the PAG project to the reticular formation of the medulla and synapse with neurons which project to the spinal cord.

5-HT turnover and the density of different 5-HT receptor subtypes can be altered by estrogen and progesterone in different areas of the brain.[55,56] The effects of progesterone on sexual behavior may be mediated by 5-HT, as depletion of endogenous 5-HT inhibits lordosis normally produced by estrogen combined with progesterone,[57] and treatment of estrogen-primed rats with progesterone increases the action of 5-HT receptor agonists on sexual response.[58] As will emerge below, the effects of serotonergic drugs, in turn, depend on the hormonal state of the female animal.

Noradrenergic pathways are also involved in the female sexual response. Genital stimulation in female rats increases firing of noradrenergic neurons[59] and disruption of noradrenergic fibers from the brainstem to the spinal cord or to the forebrain reduces lordosis.[34,60] Noradrenergic agonists applied directly to the hypothalamus increased female sexual behavior, and administration of a noradrenergic antagonist reduced sexual behavior.[61,62]

The number of oxytocin receptors in the VMN are increased by administration of progesterone in female rats following treatment with estradiol[63] and administration of oxytocin into the VMN increased lordosis in animals that had been treated with estradiol and progesterone.[64] Intracerebral injection of an oxytocin antagonist reduced both proceptive and receptive behavior of female rats.[65,66]

The Pharmacology of 5-HT and Female Sexual Function

5-HT Release

Direct administration of 5-HT into the POA and VMN inhibits sexual behavior in receptive female rats.[67] However, the actions of systemic agents are less clear-cut. Enhancers of serotonergic activity like 5-HTP, zimelidine, alaproclate, and panuramine (WY 26002) also inhibit activity in receptive animals, but stimulate lordosis in non-receptive animals.[68] The effect of 5-HT lesioning in female rats also depends on hormonal status and receptivity. Paradoxically, *p*CPA is reported to inhibit lordosis in receptive female rats and stimulate sexual behavior in non-receptive female rats.[69-71] In line with the effects of enhancing agents, destruction of 5-HT neurons with 5,7-DHT administered into the lateral ventricles, and into the VMN in particular, enhances lordotic activity, again suggesting that this is a site of inhibitory action of 5-HT on female sexual behavior.

Drug Actions at 5-HT_1 Receptors

Administration of 8-OH-DPAT or ipsapirone inhibits lordosis in female rats.[72-74] Likewise direct application of 8-OH-DPAT to the VMN in receptive female rats reduces lordosis, presumably via activation of postsynaptic 5-HT_{1A} receptors[75] (Table 6.1). Whether all 5-HT_{1A} receptor effects are postsynaptic or whether in some cases the effect may be a

presynaptic, inhibitory effect of autoreceptors on the 5-HT cell bodies, leading to reduced 5-HT release, is uncertain.

Drug Actions at 5-HT_2 Receptors

In female rats nonspecific 5-HT_2 receptor agonists such as quipazine stimulate lordosis in non-receptive female rats (Table 6.1).[68] The 5-HT_{2C} receptor antagonists pizotifen, cyproheptadine and ketanserin inhibit lordosis in ovariectomised estrogen-primed female rats.[76]

Drug Actions at 5-HT_3 Receptors

5-HT_3 antagonists such as ondansetron can increase sexual behavior in female rats.[77] This suggests that 5-HT_3 receptors may also mediate inhibitory effects of 5-HT.

Pharmacology of Sexual Function in Men and Women

The precise role of 5-HT in the etiology of sexual dysfunction in men and women is uncertain. Indeed, it is the effects of orally administered drugs with actions on serotonergic function that afford what evidence there is. Accordingly, it is not yet clear whether disturbance of spinal or brain serotonergic neurotransmission is primarily responsible for the most frequent forms of sexual dysfunction seen in clinical practice with serotonergic drugs. The balance of the findings from animal experimentation would predict inhibitory effects on sexual function from drugs enhancing 5-HT neurotransmission.

Antidepressant Drugs and Sexual Dysfunction

Reports of rates of sexual dysfunction in clinical populations vary widely (see Introduction). The main reason for such variation is the range of methods employed to collect the data. Early studies with antidepressants relied on spontaneous self-report by patients and tended to yield relatively low rates: they also failed to distinguish between rates of different forms of sexual dysfunction. Higher rates are obtained when patients are asked to fill in a questionnaire, but even under these conditions people appear reluctant to divulge sexual symptoms. Thus, the highest rates for sexual dysfunction are obtained when patients are asked sympathetically but specifically about different aspects of sexual function.

Libido

SSRIs, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) have all been reported to be associated with a reduction in sexual interest in some patients. Jacobsen[78] reported reduced libido in 21% of 160 patients treated with fluoxetine. Ten percent of his series reported decrease in libido alone, and a further 11% reported decrease in libido and decreased sexual response. A recent analysis of pooled data from several placebo-controlled trials involving nefazodone, imipramine and fluoxetine provides a useful guide for all aspects of sexual dysfunction to be described here and in the following paragraphs.[79] Decreased libido was found in 0.5% of placebo-treated patients, 0.7% of nefazodone-treated patients, 1.6% of imipramine-treated patients and 2.2% of fluoxetine treated patients. The rate of decreased libido for fluoxetine treatment was significantly greater than for placebo. The differences observed between nefazodone and fluoxetine may depend upon the 5-HT_{2C} receptor blocking effects of the former, or the more potent reuptake-blocking effects of the latter. These rates are low, reflecting the self-report design of the studies included. MAOIs have also been associated with a decrease in libido in some patients.[80]

The mechanisms by which antidepressant drugs might cause reduction in sexual desire are not established. Dopamine has been demonstrated to be involved in sexual interest and

enhanced serotonergic function in the CNS could result in diminished dopaminergic effects causing decreased libido. Some cholinergic agonists such as bethanechol have been reported to reverse the loss of sexual desire associated with TCAs such as amitriptyline,[81] underlining the possible importance of other neurotransmitter systems in mediating arousal.

Erectile Dysfunction

There may be several causes of erectile failure due to antidepressant drug treatment. Sympathetic and parasympathetic components contribute to erections. Erection occurs when venous outflow is prevented and arterioles open to allow blood to flow into the corpora cavernosa. The penis remains in its normal flaccid condition as a result of tonic α-adrenergic stimulation.

Erectile problems are not commonly reported with SSRIs but have been widely reported with TCAs and MAOIs, mainly in single-case reports or small-case series. TCAs that have been reported to cause erectile difficulties include amitriptyline, imipramine, clomipramine, desipramine, nortriptyline, and protriptyline.[82] The physiology would predict problems from excessive noradrenergic tone maintaining venous outflow or from the functionally equivalent effect of cholinergic blockade. Both effects could result from the pharmacology of the tricyclic drugs. In the analysis of pooled data on rates of sexual dysfunction in placebo-controlled studies from nefazodone trial data by Robinson,[79] erectile impotence was reported in 1.6% of the fluoxetine-treated group and 9.8% of the imipramine-treated group. The rate of erectile impotence with imipramine, but not with fluoxetine, was significantly greater than with placebo.

In a placebo-controlled study, higher rates of erectile dysfunction were reported in patients treated with phenelzine than with imipramine, although neither of these were significantly greater than placebo.[80] Moclobemide, a reversible inhibitor of MAO type A, has been reported to lead to a greater improvement in erectile function and other aspects of sexual function than doxepine in depressed patients.[83]

Priapism (prolonged and painful erections which can result in ischemia) requires emergency urological intervention and may result in permanent impairment of erectile function. This condition can occur as a result of α_1-adrenergic blockade preventing venodilatation. The clinical problem has been reported in men treated with trazodone.[84] Priapism can also occur with other psychotropic drugs including antipsychotics.

Yohimbine is an α_2-adrenoceptor antagonist, which has been successfully used in the treatment of primary erectile impotence.[85,86] It has also been used to treat erectile difficulties associated with antidepressant drugs.

Ejaculation and Orgasm

Delayed orgasm or anorgasmia appears to be a relatively common side-effect of SSRIs and is also commonly reported with TCAs and MAOIs. Impairment of orgasm has been reported in 8-75% of patients taking fluoxetine[87-90] and 6-9% of patients taking paroxetine.[91-93] These are generally likely to represent low estimates as one open study above found a much higher rate of impairment of orgasm when subjects were asked specifically about this.

Anorgasmia has been reported with all the commonly employed TCAs including clomipramine, imipramine, desipramine, nortriptyline and doxepine[81,82] and MAOIs such as phenelzine.[80] Rates of anorgasmia also vary widely in these studies. For example, in a study of sexual dysfunction in obsessive-compulsive disorder, 96% of patients treated with clomipramine described problems with orgasm![94] In another study 8.8% of patients treated with amitriptyline described delay in ejaculation.[95] Clomipramine and SSRIs have been used with reported success to *treat* premature ejaculation (e.g., ref. 96).

Delayed orgasm or anorgasmia is likely to be related to increased neurotransmission through postsynaptic 5-HT_{2C} receptors. Thus, treatment with the 5-HT antagonist cyproheptadine, which has high affinity for the 5-HT_{2C} receptor, has been found to be effective in treating SSRI-,[97,98] TCA-[99,100] and MAOI-[101,102] induced anorgasmia. However, the use of cyproheptadine has been reported to precipitate the relapse of depressive symptoms in some individuals.[101-105]

Other treatments for fluoxetine-induced anorgasmia that have been reported include yohimbine,[78] and a number of direct and indirect dopaminergic agonists. These effects are probably a result of functional antagonism of the serotonergic action of fluoxetine (or other SSRIs). By blockade of α_2-autoreceptors, yohimbine facilitates noradrenergic neurotransmission. The importance of dopaminergic input in ejaculatory function is demonstrated by the effects of direct dopaminergic agonists such as amantadine and indirect dopaminergic agonists such as dextroamphetamine and pemoline in reversing SSRI-induced anorgasmia.[106] 5-HT has an inhibitory effect on dopamine release in the brain, and dopaminergic fibers from the ventral tegmental area of the hypothalamus have been shown to mediate the ejaculatory response in the rat (see page 84).

Direct and indirect cholinergic agonists, such as neostigmine and bethanechol, have also been reported to reverse anorgasmia associated with the use of TCAs and MAOIs.[82] Successful ejaculation thus appears to depend on a balance among various cholinergic, noradrenergic, dopaminergic, and serotonergic systems.

Painful ejaculation has been reported in some men treated with TCAs.[107] This appears to be due to abnormal coordination of muscle contraction during ejaculation. Other unusual side-effects that have been reported include penile anesthesia with fluoxetine[108] and yawning and multiple orgasm with clomipramine[109] and fluoxetine.[110] A similar syndrome of yawning, stretching and ejaculation has been described in rats treated with SSRIs.

Management of Sexual Dysfunction

Management of sexual dysfunction in patients being treated with antidepressant drugs should follow a detailed assessment, including systematic inquiry into each area of sexual function, to determine its exact nature and potential cause. In particular it is important to establish whether the sexual dysfunction is a treatment-emergent side-effect of medication, or whether there may have been pre-existing sexual dysfunction related to other causes. Men may be more willing than women to describe sexual problems to a psychiatrist, and direct questioning about specific symptoms is the preferred method of inquiry.[80,111] More of a problem may be the reluctance of doctors themselves to initiate the necessary line of questioning.

General principles of psychological management include explanation and reassurance, reduction of performance anxiety, reduction of feelings of failure and resentment, and establishment of better communication between partners when addressing relationship difficulties.[112,113] This is likely to be helpful even for those patients whose sexual dysfunction is primarily drug-related. Common-sense suggests waiting for spontaneous improvement, especially in patients in the early stages of drug treatment, still recovering from depression.

Specific pharmacological approaches include reduction in dose of the offending drug, especially if this is unusually high, withdrawal (with or without substitution) of medication and drug holidays (from short-acting drugs). A problem may be the return of depressive or other symptoms. Accordingly, adjunctive drug treatments such as cyproheptadine, yohimbine, bethanecol, amantadine and pemoline are potentially useful if a variety of clinical anecdotes are correct. However, none of these adjunctive drug treatments have been

investigated in randomized, double-blind controlled studies of a specific drug-induced disorder of sexual function.

Conclusion

A primary involvement of 5-HT in the neurophysiology of sexual function is widely accepted from animal work. 5-HT probably has an important role at both a central and spinal level. There is a preliminary understanding of the mediation of the effects of 5-HT by its many receptor subtypes. Sexual dysfunction is commonly identified in the general population and is particularly described in association with mood disorder. The possible role of impaired 5-HT function as a specific etiological factor is not established beyond more general theories for the role of 5-HT in depression. Additional drug-induced sexual dysfunction is reported with a wide variety of drug treatments and is a common side effect of antidepressant drugs. Because of their relative freedom from other adverse effects, SSRIs are particularly recognized as causing sexual side-effects in some patients including reduced sexual interest, delayed ejaculation and anorgasmia. The specificity of action of the SSRIs is itself confirmatory of the role of 5-HT in human sexual function. Nevertheless, the older more non-specific TCAs may provoke even higher rates of sexual problems. An important difficulty is the failure of patients to report, and doctors to detect, sexual problems due to drugs. The management of drug-induced side-effects remains poorly worked out and is currently based on pragmatic psychological and pharmacological principles, poorly supported by systematic evidence.

References

1. WHO. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva: World Health Organization, 1992.
2. Szaz T. Sex: Facts, frauds and follies. Oxford: Blackwell, 1980:15-26.
3. Nathan SG. The epidemiology of DSM-III psychosexual dysfunctions. J Sex Marital Ther 1986; 12:267-282.
4. Malsbury CW. Facilitation of male rat copulatory behavior by electrical stimulation of the medial preoptic area. Physiol Behav 1971; 7:797-805.
5. Oaknin S, Rodriguez del Castillo A, Guerra M et al. Change in forebrain Na,K-ATPase activity and serum hormone levels during sexual behaviour in male rats. Physiol Behav 1989; 45:407-410.
6. Robertson GS, Pfaus JG, Atkinson LJ et al. Sexual behaviour increases C-FOS expression in the forebrain of the male rat. Brain Res 1991; 564:352-357.
7. Heimer L, Larsson K. Impairment of mating behavior in male rats following lesions in the preoptic anterior hypothalamic continuum. Brain Res 1966; 3:248-263.
8. Slimp JC, Hart BL, Goy RW. Heterosexual, autosexual and social behavior of adult male rhesus monkeys with medial preoptic anterior hypothalamic lesions. Brain Res 1975; 142:105-122.
9. Foreman MM, Hall JL. Effects of D2-dopaminergic receptor stimulation on male rat sexual behavior. J Neural Transm 1987; 68:153-170.
10. Bitran D, Hull EM, Holmes GM et al. Regulation of male rat copulatory behaviour by preoptic incertohypothalamic dopamine neurons. Brain Res Bull 1988; 20:323-331.
11. Warner RK, Thompson JT, Markowski VP et al. Microinjection of dopamine antagonist cis-flupenthixol into the MPOA impairs copulation, penile reflexes and sexual motivation in male rats. Brain Res 1991; 540:177-182.
12. Lal S, Guyda H, Birkadorff S. Effects of methysergide and pimozide on apomorphine-induced growth hormone secretion in men. J Clin Endocrinol 1970; 44:766-770.
13. Lal S, De La Vega CE. Apomorphine and psychopathology. J Neurol Neurosurg Psychiatry 1975; 38:722-726.

14. Lal S, Nair NPV, Cervantes P et al. Effect of naloxone or levallorphan on serum prolactin concentrations and apomorphine-induced growth hormone secretion. Acta Psychiatr Scand 1979; 59:173-179.
15. Lal S, Nair NPV, Iskandar HL et al. Effect of domperidone on apomorphine-induced growth hormone secretion in normal men. J Neural Transm 1982; 54:75-84.
16. Lal S, Ackman D, Thavundayil JX. Effect of apomorphine, a dopamine agonist, on penile tumescence in normal subjects. Prog Neuropsychopharmacol Biol Psychiatry 1984; 8:695-699.
17. Schlatter EKE, Lal S. Treatment of alcoholism with Dent's Oral Apomorphine Method. Q J Stud Alcohol 1972; 33:430-436.
18. Verma S, Chhina GS, Mohan Kumar V et al. Inhibition of male sexual behaviour by serotonin application in the medial preoptic area. Physiol Behav 1989; 46:327-330.
19. Hillegaart V, Ahlenius S, Larsson K. Region-selective inhibition of male rat sexual behavior and motor performance by localized forebrain 5HT injections: A comparison with effects produced by 8-OH-DPAT. Behav Brain Res 1991; 42:169-180.
20. Hillegaart V, Ahlenius S, Larsson K. Effects of local application of 5-HT into the median and dorsal raphe nuclei on male rat sexual and motor behavior. Behav Brain Res 1989; 33:279-286.
21. van de Kar L, Levine J, van Orden I. Serotonin in hypothalamic nuclei: Increased content after castration of male rats. Neuroendocrinology 1978; 27:186-192.
22. Marson L, McKenna KE. The identification of a brainstem site controlling spinal sexual reflexes in male rat. Brain Res 1990; 515:303-308.
23. Marson L, McKenna KE. A role for 5-hydroxytryptamine in descending inhibition of spinal sexual reflexes. Exp Brain Res 1992; 88:313-320.
24. Monaghan EP, Breedlove SM. The role of the bulbocavernosus in penile reflex behavior in rats. Brain Res 1992; 587:178-180.
25. Root WS, Bard P. The mediation of feline erection through sympathetic pathways with some remarks on sexual behavior after deafferentation of the genitalia. Am J Physiol 1947; 151:80-90.
26. Bors E, Comarr AE. Neurological disturbances of sexual function with special reference to 529 patients with spinal cord injury. Urol Surv 1960; 10:191-222.
27. Baraldi M, Benassi-Benelli A, Lolli M. Penile erections in rats after fenfluramine administration. Riv Farmacol Ter 1977; 8:375-379.
28. Foreman MM. Effects of fenfluramine and para-chloroamphetamine on sexual behavior of male rats. Psychopharmacology 1992;107:327-330.
29. Ahlenius S. Further evidence for an inhibitory role of central 5-HT in male rat sexual behavior. Psychopharmacology 1980; 68:217-222.
30. Ahlenius S. Mating behavior in the male rat treated with p-chlorophenylalanine methyl ester alone and in combination with pargyline. Psychopharmacologia(Berl) 1971; 20:383-388.
31. Salis PJ, Dewsbury DA. p-Chlorophenylalanine facilitates copulatory behavior in male rats. Nature 1971; 232:400-401.
32. Larsson K. Sexual behavior in male rats after intracerebral injection of 5,7-dihydroxytryptamine. Brain Res 1978;141:293-303.
33. McIntosh TK, Barfield RJ. Brain monaminergic control of male reproductive behavior. 1 Serotonin and the post-ejaculatory refractory period. Behav Brain Res 1984; 12:255-265.
34. Hansen S, Ross SB. Role of descending monoaminergic neurones in the control of sexual behavior. Effects of intrathecal infusion of 6-hydroxydopamine and 5,7-dihydroxytryptamine. Brain Res 1983; 268:285-290.
35. Svensson L. Spinal monoaminergic modulation of masculine copulatory behavior in the rat. Brain Res 1984; 302:315-321.
36. Berendsen HHG. Involvement of 5-HT1C receptors in drug-induced penile erections in rats. Psychopharmacology 1990; 101:57-61.
37. Ahlenius SK, Larsson L, Svensson S et al. Effects of a new type of 5-HT receptor agonist on male rat sexual behaviour. Pharmacol Biochem Behav 1981; 15:785-792.

38. Goodwin GM, Green AR. A behavioural and biochemical study in mice and rats of putative agonists and antagonists for 5-HT1 and 5-HT2 receptors. Br J Pharmacol 1985; 84:743-753.
39. Pomerantz SM. Serotonergic influences on male sexual behavior of rhesus monkeys: Effects of serotonin agonists. Psychopharmacology 1993; 111:47-54.
40. Hansen S. Spinal control of sexual behavior: Effects of intrathecal administration of lisuride. Neurosci Lett 1982; 33:329-332.
41. Szele FG, Murphy DL, Garrick NA. Effects of fenfluramine, m-chlorophenylpiperazine, and other serotonin -related agonists and antagonists on penile erections in non-human primates. Life Sci 1988; 43:1297-1303.
42. Gower AJ, Berendsen HHG, Broekkamp CLE. Antagonism of drug-induced yawning and penile erections in rats. Eur J Pharmacol 1986; 122:239-244.
43. Berendsen HHG, Broekkamp CLE. Drug-induced penile erections in rats. Eur J Pharmacol 1987; 135:279-287.
44. Mas M. Stimulation of spinal serotonergic receptors facilitates seminal emission and suppresses penile erectile reflexes. Brain Res 1985; 342:128-134.
45. Steers WD, De Groat WC. Effects of m-chlorophenylpiperazine on penile and bladder function in rats. Am J Physiol 1989; 257:R1441-R1449.
46. Pfaff DW, Sakuma Y. Deficit in the lordosis reflex of female rats caused by lesions in the ventromedial nucleus of the hypothalamus. J Physiol 1978; 288:203-210.
47. Rubin BS, Barfield RJ. Priming of estrous responsiveness by implants of 17β-estrodiol in the ventromedial hypothalamic nucleus of rats. Endocrinology 1980; 106:504-509.
48. Pleim ET, Barfield RJ. Progesterone versus estrogen facilitation of female sexual behavior by intracranial administration to rats. Horm Behav 1988;22: 150-159.
49. Blaustein JD, Feder HH. Cytoplasmic progestin receptors in guinea pig brain: Characteristics and relationships to the induction of sexual behavior. Brain Res 1979; 169:481-497.
50. Sakuma Y, Pfaff DW. Facilitation of female reproductive behavior from mesencephalic central gray in the rat. Am J Physiol 1979; 237: R278-R284.
51. Sakuma Y, Pfaff DW. Mesencephalic mechanism for integration of female reproductive behaviour in the rat. Am J Physiol 1979; 237: R285-R290.
52. Sakuma Y, Pfaff DW. Convergent effects of lordosis-relevant somatosensory and hypothalamic influences on central gray cells in the rat mesencephalon. Exp Neurol 1980; 70:269-281.
53. Sakuma Y, D.W. P. Excitability of female rat central gray cells and medullary projections: Changes produced by hypothalamic stimulation and estrogen treatment. J Neurophysiol 1980; 44:1012-1023.
54. Hennessey AC, Camak L, Gordon E et al. Connections between the pontine central gray and the ventromedial hypothalamus are essential for lordosis in female rats. Behav Neurosci 1990; 104:477-488.
55. Biegon A, Fishette CT, Rainbow TC et al. Serotonin receptor modulation by estrogen in discrete brain nuclei. Neuroendocrinology 1982; 35:287-291.
56. James MD, Hole DR, Wilson CA. Differential involvement of 5-hydroxytryptamine (5HT) in specific hypothalamic areas in the mediation of steroid-induced changes in gonadotrophin release and sexual behaviour in female rats. Neuroendocrinology 1989; 49:561-569.
57. Wilson CA, Bonney RC, Everard DM et al. Mechanisms of action of p-chlorophenylalanine in stimulating sexual receptivity in the female rat. Pharmacol Biochem Behav 1982; 16:777-784.
58. Sietnieks A, Meyerson BJ. Enhancement by progesterone of 5-hydroxytryptophan inhibition of the copulatory response in the female rat. Neuroendocrinology 1982; 35:321-326.
59. Crowley WR, Rodriguez-Sierra JF, Komisaruc BR. Monoaminergic mediation of the antinociceptive effect of vaginal stimulation in rats. Brain Res 1977; 137:64-84.
60. Hansen S, Stanfield EJ, Everitt BJ. The role of ventral bundle noradrenergic neurones in sensory components of sexual behaviors and coitus-induced pseudopregnancy. Nature 1980; 286:152-154.
61. Crowley WR, Nock B, Feder HH. Facilitation of lordosis behavior by clonidine in female guinea pigs. Pharmacol Biochem Behav 1978; 8:207-209.
62. Fernandez-Guasti A, Larsson K, Beyer C. Potentiative action of α- and β-adrenergic receptor stimulation in inducing lordosis behavior. Pharmacol Biochem Behav 1985; 22:613-617.

63. Schumacher M, Coirini H, Pfaff DW et al. Behavioral effects of progesterone associated with rapid modulation of oxytocin receptors. Science 1990; 250:691-694.
64. Schumacher M, Coirini H, Frankfurt M et al. Localised actions of progesterone in hypothalamus involve oxytocin. Proc Natl Acad Sci USA. 1989; 86:6798-6801.
65. Witt DM, Insel TR. A selective oxytocin antagonist attenuates progesterone facilitation of female rat sexual behavior. Endocrinology 1991; 128:3269-3276.
66. McCarthy RA, Kleopoulos SP, Mobbs CV et al. Infusion of antisense oligodeoxynucleotides to the oxytocin receptor in the ventromedial hypothalamus reduces estrogen-induced sexual receptivity and oxytocin receptor binding in the female rat. Neuroendocrinology 1994; 59:432-440.
67. Foreman MM, Moss RL. Role of hypothalamic serotonergic receptors in the control of lordosis behavior in the female rat. Hormone Res 1978;10:97-106.
68. Hunter AJ, Hole DR, Wilson CA. Studies into the dual effects of serotonergic pharmacological agents on female sexual behaviour in the rat: Preliminary evidence that endogenous 5HT is stimulatory. Pharmacol Biochem Behav 1985; 22:5-13.
69. Segal DS, Whalen RE. Effect of chronic administration of p-chlorophenylalanine on sexual receptivity of the female rat. Psychopharmacologia 1970; 16:434-438.
70. Gorzalko BB, Whalen RE. Inhibition not facilitation of sexual behaviour by PCPA. Pharmacol Biochem Behav 1975; 3:511-513.
71. Al Sati M, Aron CL. Role played by serotonin in the control of oestrus receptivity, ovarian activity and ovulation in the cyclic female rat. Psychoneuroendocrinology 1981; 6:121-129.
72. Ahlenius S, Fernandez-Gausti A, Hjorth S et al. Suppression of lordosis behavior by the putative 5-HT receptor agonist 8-OH-DPAT in the rat. Eur J Pharmacol 1986; 124:361-363.
73. Mendelson SD, Gorzalka BB. 5HT1A receptors: Differential involvement in female and male sexual behavior in the rat. Physiol Behavior 1986; 37:345-351.
74. Fernandez-Guasti A, Ahlenius S, Hjorth S et al. Separation of dopaminergic and serotonergic inhibitory mechanisms in the mediation of estrogen-induced lordosis behavior in the rat. Pharmacol Biochem Behav 1987; 27:93-98.
75. Uphouse L, Montanez M, Richards-Hill R et al. Effects of 8OH-DPAT on sexual behaviours of the proestrus rat. Pharmacol Biochem Behav 1991; 39:635-640.
76. Mendelson SD, Gorzalka BB. Serotonin type 2 antagonists inhibit lordosis behavior in the female rat: reversal with quipazine. Life Sci 1986; 38:33-39.
77. Wilson CA. Pharmacological targets for the control of male and female sexual behaviour. In: Riley APM, Wilson C, ed. Sexual Pharmacology. Oxford: Oxford Medical Publications, 1993:1-58.
78. Jacobsen FM. Fluoxetine-induced sexual dysfunction and an open trial of yohimbine. J Clin Psychiatry 1992; 53:119-122.
79. Robinson DS, Roberts DL, Smith JM et al. The safety profile of nefazodone. J Clin Psychiatry 1996; 57:31-38.
80. Harrison WM, Rabkin JG, Ehrhardt AA et al. Effects of antidepressant medication on sexual function: a controlled study. J Clin Psychopharmacol 1986; 6:144-149.
81. Seagraves RT. Treatment emergent sexual dysfunction in affective disorder: A review of management strategies. J Aff Disord 1993; 11:57-60.
82. Baldwin DS. Psychotropic drugs and sexual dysfunction. Int Rev Psychiatry 1995; 7:261-273.
83. Philipp M. A comparison study of moclobemide and doxepin in major depression with special reference to effects on sexual dysfunction. Int Clin Psychopharmacol 1993; 7:149-153.
84. Banos JE, Bosch F, Farre M. Drug-induced priapism. Its aetiology, incidence and treatment. Med Toxicology 1989; 4:46-58.
85. Reid K, Morales A, Herris C et al. Double blind trial of yohimbine in treatment of psychogenic impotence. Lancet 1987; 2:421-423.
86. Nelson RP. Non-operative management of impotence. J Urology 1987; 137:1168-1172.
87. Herman JB, Brotman AW, Pollack MH et al. Fluoxetine-induced sexual dysfunction. J Clin Psychiatry 1990; 51:25-27.
88. Musher JS. Anorgasmia with the use of fluoxetine. Am J Psychiatry 1990; 147:948.

89. Zajecka J, Fawcett J, Schaff M et al. The role of serotonin in sexual dysfunction: Fluoxetine-associated orgasm dysfunction. J Clin Psychiatry 1991; 52:66-68.
90. Patterson WM. Fluoxetine-induced sexual dysfunction. J Clin Psychiatry 1993; 54:71.
91. Dunbar GC, Cohn JB, Abre LF et al. A comparison of paroxetine, imipramine and placebo in depressed outpatients. Br J Psychiatry 1991; 159:394-398.
92. Feighner JP. A double-blind comparison of paroxetine, imipramine and placebo in depressed outpatients. Int Clin Psychopharmacology 1992; 6:31-35.
93. Jenner PN. Paroxetine: An overview of dosage, tolerability and safety. Int Clin Psychopharmacology 1992; 6:69-80.
94. Monteiro WO, Norshirvani HF, Marks IM. Anorgasmia from clomipramine in obsessive compulsive disorder: a controlled trial. Br J Psychiatry 1987; 151:107-112.
95. Doogan DP. Toleration and safety of sertraline: experience worldwide. Int Clin Psychopharmacol 1991; 6:47-56.
96. Althof SE, Levine SB, Corty W. A double-blind crossover trial of clomipramine for rapid ejaculation in 15 couples. J Clin Psychiatry 1995; 56:402-407.
97. Cohen AJ. Fluoxetine-induced yawning and anorgasmia reversed by cyproheptadine treatment. J Clin Psychiatry 1992; 53:174.
98. McCormick S, Olin J, Brotman AW. Reversal of fluoxetine-induced anorgasmia by cyproheptadine in two patients. J Clin Psychiatry 1990; 51:383-384.
99. Sovner R. Treatment of tricyclic antidepressant-induced orgasmic inhibition with cyproheptadine. J Clin Psychopharmacol 1984; 4:169.
100. Steele TE, Howell EF. Cyproheptadine for imipramine-induced anorgasmia. Clin Psychopharmacol 1986; 6:326-327.
101. Riley AJ, Riley EJ. Cyproheptadine and antidepressant-induced anorgasmia. Br J Psychiatry 1986; 148:217-218.
102. Zubieta JK, Demitrack MA. Depression and cyproheptadine: MAOI treatment. Biol Psychiatry 1992; 31:1177-1178.
103. Feder R. Reversal of antidepressant activity of fluoxetine by cyproheptadine in three patients. J Clin Psychiatry 1991; 52:163.
104. Goldbloom DS, Kennedy SH. Adverse interaction of fluoxetine and cyproheptadine in two patients with bulimia nervosa. J Clin Psychiatry 1991; 52:261-262.
105. Hollander E, McCarley A. Yohimbine treatment of sexual side effects induced by serotonin reuptake blockers. J Clin Psychiatry 1992; 53:207-209.
106. Gitlin MJ. Psychotropic medications and their effects on sexual function: Diagnosis, biology, and treatment approaches. J Clin Psychiatry 1994; 55:406-413.
107. Aizenberg D, Zemishlany Z, Hermesh H et al. Painful ejaculation associated with antidepressants in four patients. J Clin Psychiatry 1991; 52:461-463.
108. Neill JR. Penile anaesthesia associated with fluoxetine. Am J Psychiatry 1991; 148:1603.
109. McLean JG, Forsythe RG, Kapkin IA. Unusual side effects of clomipramine associated with yawning. Can J Psychiatry 1983; 28:569-570.
110. Modell JG. Repeated observations of yawning, clitoral engorgement and orgasm associated with fluoxetine administration. J Clin Psychiatry 1989; 9:63-65.
111. Shen WW, Sata LS. Inhibited female orgasm resulting from psychotropic drugs: A five-year update. J Reproductive Med 1990; 35:11-14.
112. Hawton K. Sex Therapy: A Practical Guide. Oxford: Oxford University Press, 1985.
113. Bancroft J. Human sexuality and its problems. 2nd ed. Edinburgh: Churchill Livingstone, 1989.

Chapter 7

SSRIs and Suicide

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The selective serotonin reuptake inhibitors (SSRIs) have increased in popularity and extent of use since their introduction. At the same time, our knowledge concerning the relationship between suicide and depression has increased. The impact of this group of drugs on this knowledge has been considerable. An additional consideration is that, as with all drugs and particularly with antidepressants, they are liable to be taken in overdose. This chapter reviews some of the links between the SSRIs and depression, overdose and suicide.

The Relationship Between Depression and Suicide

Depression is a common disorder. Estimates of the 12-month prevalence rate for diagnosed depression in the USA range from 20 to 250 per 1000.[1,2] Each year, 2-3 million people in Britain suffer from depression requiring medical care.[3,4] This is equivalent to a 12-month prevalence rate of 30-50 per 1000.[3,4] Depression is associated with a risk of suicide between 13-30 times higher than for the overall population.[5] This figure does not include those with undiagnosed depression. For 60-70% of suicides, the available evidence shows that the individual was probably depressed[6-8] and depression accounts for about 4000 deaths from suicide each year in Britain alone. To put it another way, 7.5 of each 1000 men and 3 of each 1000 women are likely to commit suicide while depressed. To this may be added some of the 30-40% of suicides that occur in apparently non-depressed people, since many of these may also have undiagnosed depression.

In both the USA[9] and Britain,[10] suicide is the eighth commonest cause of death. National differences in suicide rates are probably mainly due to social and cultural differences in support, and to variations in the social acceptability of death by suicide, but these differences appear to be slowly diminishing. The human cost of suicide is high. It occurs most commonly in the young, being the 2nd or 3rd leading cause of death in 15-34 year olds in most countries.[11] and the third most important contributor to life years lost. However, although the relative importance of suicide is greater in younger adults, the actual risk is greater in older people. In most countries the peak for suicides occurs in midlife in women, and ages 75 or older in men.[11]

Since it is known that depression and suicide are linked, it might seem sensible to prescribe antidepressant drugs not only to relieve depressive illness, but also to prevent suicide, its most drastic outcome. Although adequate documentation is lacking and there is as yet no evidence that the suicide rate has fallen since the introduction of antidepressants, it is widely assumed that the effective treatment of depression can and does prevent suicide; evidence from a study in Gotland, Sweden strongly supports this concept.[12]

The doctor treating the depressed patient, especially where there is evidence that the patient has considered suicide as an option, is faced with a therapeutic dilemma. Antidepressant drugs are currently the mainstay of treatment for all but the mildest forms

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of depression. Nevertheless, in the UK, the most common method of suicide is by self-poisoning and antidepressants account for a large proportion of these deaths. In 1992, 9% of poisoning deaths in England and Wales[10] were due to antidepressant overdose. In other countries, the figure may be higher; in Norway, 20% of all fatal poisonings were attributed to antidepressants.[13] Around one-third of people diagnosed with depression are given antidepressants.[14] Overall it has been estimated that about 1% of depressed patients prescribed antidepressants will make an attempted or completed act of suicide.[15] About one-third of these will use the drug prescribed.[16] So the doctor who is providing his patient with a potential means of committing suicide has a duty to consider the suicide risk of his patient and the potential overdose toxicity of the prescription. Some antidepressants are less likely to be used in overdose than others[17,18] and the antidepressants differ in their degree of toxicity. While antidepressants are currently only prescribed for a small proportion of those who are depressed, this number is increasing as a result of campaigns such as those by The Royal Colleges of Psychiatrists and General Practitioners in the UK and the National Institute for Mental Health the USA. However, suicide prevention is clearly not the only consideration when treating depressed people. Suicide is by no means an inevitable outcome of depression and while some antidepressants may be more appropriate than others on the basis of suicidality, the prescribing choice may also be influenced by other factors. Those antidepressants which are best suited to the suicidal patient in terms of toxicity in overdose may have side-effects which, although mild, are undesirable for the individual.

It is notoriously hard to predict which depressed individuals will commit suicide,[19-22] even under close supervision within a hospital environment. The severity of the depressive illness is a poor indicator. Nonetheless the broad statistical picture suggests that suicide attempts are twice as frequent in patients with recurrent brief depression as in those with major depressive disorders.[23] Fifteen percent of patients suffering from severe depression ultimately die by suicide;[24,25] they are probably more likely than those with milder depression to succeed at the first attempt.

Most antidepressant overdoses, whether fatal or not, occur outside hospital; 70-80% of patients dying from tricyclic antidepressant (TCA) overdose do so before reaching hospital.[26] In a considerable proportion of suicide attempts the subjects never make contact with medical services of any kind.[27] The safety record of the SSRIs in overdose[28-30] suggests that the percentage who reach hospital alive is likely to be much higher for this group of drugs, but might be confounded by fewer patients presenting to hospital. Actual data are lacking.

Evidence Linking 5-HT Dysfunction and Suicide

The SSRIs share a common mechanism of action, despite their remarkably differing chemical structures (fluvoxamine is a monocyclic agent, fluoxetine a bicyclic agent, sertraline a naphthylamine derivative, paroxetine a phenyl piperidine derivative and citalopram a bicyclic isobenzo-furan derivative). The number of deaths per million prescriptions of antidepressants has been shown to be inversely related to their serotonin (5-HT) reuptake inhibition activity[31] but this relationship may be coincidental with their structural properties, since the TCAs tend to have higher fatal toxicity in overdose.

Several studies have reported there to be fewer imipramine binding sites (indicative of the 5-HT transporter) in the frontal cortex of individuals who have committed suicide[32] than in those of sudden accident victims. They also have low levels in their cerebrospinal fluid (CSF) of the 5-HT metabolite, 5-hydroxyindole acetic acid (5-HIAA).[33,34] These pieces of evidence suggest that drugs which inhibit the reuptake of 5-HT could play a part in the prevention of suicide possibly over and above their antidepressant effect.

Comparison of Consequences of Overdose of SSRIs versus Other Antidepressant Agents

Comparing the toxicity of antidepressants in overdose is not a simple matter because the mechanisms of toxicity vary between classes of drugs and also between individual drugs in the different classes. Animal experiments often give a strong indication of potential toxicity and, in some cases, correlate well with the estimates of human toxicity, but their predictive value for newly marketed drugs cannot be relied upon. Epidemiological studies from several countries have provided evidence of marked differences in overdose toxicity between drug groups and, in some cases, between individual drugs, with some of the older tricyclic drugs being the most toxic. Eighty percent of all deaths arising from overdose of antidepressant medication in the UK are caused by two TCAs: amitriptyline and dothiepin. These drugs are each associated with around 50 overdose deaths per million prescriptions while the TCAs as a group are associated with 36 deaths per million prescriptions in Britain.[35] Taken alone these figures convey little information about the relative toxicity of either drug, but simply suggest that when a sufficient amount is taken in overdose, they can cause death. However, considered within an epidemiological context, they suggest that both drugs are highly toxic in overdose, a suggestion which is supported by animal studies of the toxicity of TCAs and by clinical evidence of overdose toxicity. Most of the older TCAs have a narrow therapeutic window. Many could be life-threatening in a single dose of 15-20 mg/kg, which means that 14 x 75 mg tablets could prove fatal for an adult if taken in a single overdose, a number likely to be dispensed in a single prescription. Bolster et al,[36] in their 5-year review of fatal self-ingested overdoses in Scotland, found that in 8 of 24 overdoses involving amitriptyline the general practitioner had recently prescribed over 100 tablets on one prescription.

The frequency with which a drug causes fatal poisoning when taken in overdose depends on three factors. First, the intrinsic potential of that drug to cause acute fatal poisoning in humans, second, its availability in the population, and third, the dose taken. National mortality data can be a useful indicator of toxicity, and have been used in the creation of a fatal toxicity index, which is derived from a measure of the availability of the drug in the community, together with an estimate of the number of deaths attributed to overdose from each drug. While many countries have a reasonably well developed system of recording causes of death, it is less easy to obtain reliable data on the availability of a drug in a given population. In the UK, where such data are available, a fatal toxicity index has been produced by several authors.[35,37-40] The index uses publicly available national mortality data, and prescription data, which are obtainable on request. The Fatal Toxicity Index (FTI) can be defined as:

$$\text{FTI} = \frac{\text{number of deaths associated with drug}}{\text{number of prescriptions for drug}}$$

Using this formula, several studies have, in recent years, highlighted differences in the overdose toxicity of the available antidepressant drugs.[35,37-40] As with other epidemiological methods, the FTI cannot provide an absolute measure of toxicity, and the use of national data has shortcomings. There may be systematic errors in mortality data; for example, some drugs (such as the monoamine oxidase inhibitors: 'MAOIs') may not be detectable by post-mortem analysis, while a number of antidepressant drugs are the active metabolite of another drug. However, the coroner also draws upon other lines of evidence. The FTI cannot take into account: the quantities of drugs and other substances actually taken (rather than prescribed) and the medical condition of the patients; confounding by prescriber biases

or patient biases (such as the inability to distinguish between the use of first-line and second-line drugs); and confounding from antidepressant use for other indications. But while small differences in suicide rates during treatment with different antidepressants could be due to chance or unsatisfactory matching between groups, the use of national data increases the number of FTI values which reach statistical significance and these are more likely to reflect real differences. Importantly, most biases run in favor of the TCAs, which are more widely used as first-line therapy and have a narrower therapeutic window than the newer antidepressants. It is also possible that SSRIs are selectively prescribed to people at greater risk of overdose. Hence the FTI provides a useful and clinically relevant indication of fatal toxicities; the development of alternatives which address all the shortcomings is not practical.

Human Data

In the UK, three studies have presented data based on the number of deaths recorded as overdose per million prescriptions of prescribed antidepressants.[31,35,41] The studies referred to mortality tables published by the Office of Population Censuses and Surveys on drug-associated deaths in England, Wales and Scotland, and corrected the figures obtained using relevant Department of Health data on prescription rates. Only deaths reportedly caused by a single drug were included. The χ^2 test was applied to the groups of antidepressants. The expected numbers of deaths were given for the individual drugs with Fisher's exact test (one-tailed) applied to the data. Confidence limits were calculated as the mean ± 1.96 standard deviations for each drug.

The data show that for the period 1976-1984, the older TCAs such as dothiepin, amitriptyline, desipramine and nortriptyline had the highest FTI (the number of deaths due to overdose per million prescriptions).[41] When estimated for the period 1987-1992, the analysis revealed that the SSRIs fluoxetine, paroxetine and sertraline had low lethality in overdose (Table 7.1).[35] The same study also showed that TCAs were implicated in most deaths, with two drugs, amitriptyline and dothiepin, accounting for 81.6% of all deaths. As a group, the older TCAs were associated with a significantly higher number of deaths per million prescriptions than all the other antidepressants taken together ($P<0.001$) (Table 7.2). By contrast, the lowest number of deaths per million prescriptions was attributed to the SSRIs ($P<0.001$).

Figures such as these strongly suggest that in the event of overdose, the TCAs as a group and in particular the older TCAs are significantly more likely to prove fatally toxic than other groups of antidepressants. The same conclusion was reached by four further studies, conducted in Norway,[42] Finland,[43] Sweden,[44] and the United States,[45] respectively. Each study obtained data on suicide by antidepressant poisoning from national government statistics, and corrected the figures obtained using differences in prescription rates published by official sources; only a restricted range of antidepressants is available in Scandinavia. The Norwegian study obtained information regarding suicides by antidepressant poisoning from the Central Bureau of Statistics, and the prescription data from the Norwegian Medicine Depot. This study found that amitriptyline and doxepin were more likely to lead to death by poisoning than the non-tricyclic antidepressant, mianserin. The Finnish study obtained data on suicides by antidepressant overdose from medical examiners throughout the country and the prescriptions data were obtained from the National Board of Health. This study also concluded that amitriptyline and doxepin carried a higher risk of death by poisoning than mianserin. The Swedish study, which investigated all suicides in southern Sweden between 1986-1989 in which antidepressant drugs were found in the blood, determined that amitriptyline was the agent most commonly involved.[44] When the figures were corrected for sales, trimipramine was the most frequently involved causal agent (Table 7.3). A 5-year

Table 7.1. Number of deaths per million prescriptions between 1987 and 1992 for antidepressant drugs in England, Wales, and Scotland

Antidepressants	Year introduced in the UK	Observed deaths	Expected deaths (from mean of all drugs)	Deaths per million prescriptions (95% confidence intervals)*
Tricyclic antidepressants				
Amoxapine	1989	13	2	157.18 (83.35-254.23)
Desipramine	1963	3	1	75.76 (14.28-185.74)
Nortriptyline	1963	19	11	51.77 (31.11-77.67)
Dothiepin	1969	801	504	47.86 (44.60-51.23)
Amitriptyline	1961	509	394	38.94 (35.63-42.39)
Imipramine	1959	111	106	31.54 (25.95-37.68)
Doxepin	1969	37	46	23.99 (16.89-32.35)
Trimipramine	1966	34	73	13.93 (9.64-19.01)
Clomipramine	1970	26	108	7.26 (4.74-10.32)
Iofepramine	1983	10	125	2.42 (1.15-4.14)
Protriptyline	1966	0	4	0.00
Iprindole	1968	0	1	0.00
Butriptyline	1975	0	0	0.00
Monoamine oxidase inhibitors				
Tranylcypromine	1960	8	9	27.87 (11.90-50.54)
Phenelzine	1959	4	15	7.86 (2.04-50.54)
Isocarboxazid	1960	0	3	0.00
Iproniazid	1958	0	0	0.00

Table 7.1. Number of deaths per million prescriptions between 1987 and 1992 for antidepressant drugs in England, Wales, and Scotland

Antidepressants	Year introduced in the UK	Observed deaths	Expected deaths (from mean of all drugs)	Deaths per million prescriptions (95% confidence intervals)*
Atypical antidepressants				
Viloxazine	1974	1	0	63.17 (0.03-247.66)
Maprotiline	1974	6	11	16.22 (5.84-31.80)
Trazodone	1980	7	27	7.83 (3.10-14.70)
Mianserin	1976	12	88	4.11 (2.11-6.76)
Selective Serotonin Reuptake Inhibitors				
Sertraline	1990	1	5	6.23 (0.00-24.43)
Fluvoxamine	1987	2	13	4.78 (0.45-13.71)
Paroxetine	1991	1	12	2.60 (0.00-10.18)
Fluoxetine	1989	1	46	0.66 (0.00-2.58)
All antidepressants		1606		30.10

* Confidence intervals were calculated as the mean value ± standard deviations for each drug.
Based on Ref. 35.

Table 7.2. Fatal poisonings and deaths per million prescriptions for deaths from single antidepressants between 1987 and 1992, by class of drug

Antidepressant class	Observed deaths	Expected deaths	No. of prescriptions (millions)	χ^2 value	Deaths per million prescriptions (95% CI)*
Tricyclic antidepressants	1563	1378	45.78	24.80	34.14 (32.47-35.86)
Monoamine oxidase inhibitors	12	27	.89	8.17	13.48 (6.93-22.19)
Atypical antidepressants	26	126	4.20	79.78	6.19 (4.04-8.80)
Selective serotonin reuptake inhibitors	5	75	2.48	54.99	2.02 (0.64-4.17)
All antidepressants	1606		53.55		30.10

* Confidence intervals (CI) were calculated as the mean value ± 1.96 standard deviations for each drug.
Based on Ref 35.[4]

study of a UK general practice database confirmed these findings. Fluoxetine was responsible for almost half the number of deaths per person years at risk than dothiepin, and also fewer than amitriptyline.[46]

Animal Data

In assessing the relative safety of a given antidepressant when taken in overdose, it may be of value to consider acute lethal doses of antidepressants given orally to animals. In spite of pharmacokinetic and metabolic differences which may exist between animal species, there is some correlation between the order of acute toxicity of an antidepressant (as indicated by the median lethal dose (LD_{50}) following oral administration) and its rank order in the Fatal Toxicity Index score.[47,48] Prior to the widespread use of a drug, there may be no other indication of its overdose toxicity than the results of animal studies. The correlation with the FTI indicates that animal data can provide a preliminary indication of the potential overdose toxicity in humans of a drug before it has been available for a sufficient number of years to generate a statistically significant FTI value. Also, animal data can be used to support FTI data when there is concern about confounding and biases. But animal toxicity studies are no substitute for human data which can be derived from epidemiological studies following the introduction of a drug.

Table 7.3. Sales-corrected distribution [using the number of defined daily doses (DDDs) sold] of antidepressant drugs amongst cases of suicide or possible suicide in Sweden between 1986 and 1989

Antidepressant	Number of cases	Number of cases divided by DDDs per 1000 inhabitants per day
Amitriptyline	70	24.0
Clomipramine	12	7.5
Imipramine	5	12.5
Lofepramine	1	0.7
Maprotiline	8	4.9
Nortriptyline	4	6.7
Trimipramine	11	32.4

Based on Ref. 44.

Fatality Rates

Not all overdoses are fatal. The observed differences between antidepressants as to their prescription/fatality ratio could have two possible explanations: either that, when taken in overdose, case-fatality rates vary for each drug, or that rates of attempted overdose vary with each drug. Of the two possibilities, evidence is strongest for the first hypothesis, namely that case-fatality rates differ between antidepressants because of objective inherent differences in toxicity.

In the USA, using relevant data for the period 1989-1990, Kapur and colleagues found that, in the event of overdose, the comparative risk of death was significantly greater with the older antidepressants than with the newer antidepressants (Table 7.4).[45] Data obtained both from the National Institute on Drug Abuse and the Association of Poison Control Centers showed that desipramine was associated with significantly more deaths per overdose attempt than other TCAs.

The total mortality rate generally accepted for all antidepressants, excluding the SSRIs, when taken in overdose is 2-3%[49,50] with an in-patient mortality for tricyclic overdose in the USA estimated at 0.6-15.2%.[48,50] In a questionnaire analysis of general practice patients, 246 out of 42,082 (0.6%) amitriptyline patients had attempted suicide with their antidepressant. Four patients who overdosed with amitriptyline alone died, and intensive care was necessary for 56 survivors of amitriptyline overdose.[16]

Treatment for an overdose patient taken to hospital involves accident and emergency care including resuscitation and gastric decontamination, and hospital stay in ward and intensive therapy unit, as well as psychiatric assessment and counseling. The TCAs are more likely than the other antidepressants to lead to medical complications when taken in overdose.[51] A proportion of TCA and MAOI overdose patients will have a lengthy stay in

Table 7.4. Relative risk of death (with 95% confidence intervals) from overdose with antidepressants in the U.S.A.

Drug	Association of Poison Control Centers (trazodone = 1.00)[a]	National Institute on Drug Abuse (fluoxetine = 1.00)[b]
Desipramine	16.88 (8.16-36.13)	8.5 (1.82-26.53)
Nortriptyline	8.63 (3.69-20.59)	8.6 (3.69-20.59)
Amitriptyline	6.06 (2.51-14.80)	2.5 (0.51-9.60)
Imipramine	7.53 (3.18-18.15)	2.5 (0.42-11.46)

[a]; based on suicide reports from Poison Control Centers for 1989 and 1990.
[b]; based on suicide reports from the National Institute on Drug Abuse for 1989.
Based on Ref. 45.

intensive therapy unit wards and hospital; SSRI overdose patients do not. Although in one study, of 37 patients who took overdoses of fluoxetine alone, 10 were admitted to an intensive therapy unit with a mean time to discharge of 24.4 hours,[49] experience of overdose with this drug was limited at the time.

Mechanisms of Toxicity of the Different Drug Types

We compare here some of the tricyclic and other antidepressant drugs with the SSRIs.

Tricyclic Agents

It has now been established that the mechanism of toxicity in TCA overdose is the membrane-stabilizing (quinidine-like) activity of these drugs,[52] a property which non-tricyclic drugs do not possess to any significant degree.[53] This property of the TCAs can lead to death from cardiac arrhythmias and hypotension. Recommended management for any intensity of tricyclic overdose has in the past involved admission to a cardiac-monitored bed for at least 72 h. In the 1980s, attempts were made to modify management for low risk cases and so reduce the burden on hospitals.[50] but over 50% of tricyclic overdoses are associated with significant cardiac complications.[51] An Australian study[54] investigated 287 patients who had been admitted to hospital with TCA poisoning. The various types of TCA were ingested roughly in proportion to their market share in Australia. Generalized seizures were more likely after dothiepin than after other TCAs (9/67 versus 5/220), as were cardiac arrhythmias (4/67 versus 3/220). The difference was not related to the size of the ingested dose, characteristics of the patients or coingestion of other substances. The odds ratio for seizures with dothiepin versus other TCAs was 6.7 (95% confidence limit : 2.2-20.7). The authors concluded that dothiepin is of high intrinsic toxicity, and appears to be proconvulsant in overdose. There has however, been some debate regarding the conclusion of this study. [55,56]

Amoxapine is an atypical tricyclic drug. Cardiotoxicity is low, but overdose of amoxapine tends to induce convulsions, hyperthermia and rhabdomyolysis.[57] While these effects had been recognized for a number of years, it was not until amoxapine was marketed in Britain

and compared with other antidepressants that it was seen to have the highest FTI of any antidepressant with 153 deaths per million prescriptions.[35] Since then it has no longer been actively marketed.

Clomipramine, with a typical tricyclic structure, ranks fairly low on the toxicity index.[37] A number of possible explanations have been suggested,[31,37] among them that clomipramine is widely prescribed for patients with obsessive-compulsive disorder, who are at lower risk of attempting suicide than some other groups of depressed patients. In addition, the mode of action of this drug is mainly through inhibition of 5-HT reuptake: the SSRIs have been associated with a reduction in suicidal ideation.[31]

Lofepramine, an atypical tricyclic drug, has relatively low toxicity in overdose and has consistently had a remarkably low FTI in the studies which have been carried out.[31]

SSRIs

The SSRIs have the lowest toxicities in overdose of the antidepressant agents considered in this chapter. This accords with clinical experience.[28-30] There are numerous cases where patients have survived large overdoses of SSRIs with minimal or no evidence of serious organ dysfunction.

Fluvoxamine appears to have low toxicity in overdose. Symptoms are often minimal: nausea, vomiting, dizziness and somnolence. Patients are often symptom-free within 24-48 h. There is one reported case of prolonged cerebral depression after ingestion of 5.5 g. Overdoses of up to 9 g have been reported with minimal symptoms and full recovery. Only two deaths from overdose with fluvoxamine alone had been reported in the literature by 1992, with an estimated patient exposure of 4.5 million individuals. [31]

There are similar figures for the other SSRIs: by 1995 there were two overdose deaths due to paroxetine alone out of over 7.5 million patients treated.[32]

The didemethyl metabolite of citalopram prolongs the QT interval in dogs, and these animals may also have seizures after large doses of citalopram. One report from Sweden has suggested that citalopram was responsible for 6 overdose deaths.[58] However, with a low level of metabolite in these cases, and no evidence of seizures, some authors have questioned whether citalopram was indeed the cause of death.[59] Other drugs were present in low doses at autopsy, and citalopram was in most cases found in the stomach, only partially absorbed, and it may be that the true cause of death was not determined. This is particularly likely since there are no other reports of deaths by overdose with citalopram, which is the most widely prescribed antidepressant drug in Sweden. Case reports such as this without any form of comparator are unhelpful, though they might in some cases provide a useful early warning. In the case of citalopram there are no further data at present. Comparative data are needed to put the potential for fatal toxicity due to citalopram overdose in perspective.

Atypical Antidepressants

Often classed as an 'atypical' antidepressant, maprotiline nevertheless has a bridged tricyclic structure and, in terms of adverse effects and toxicity, resembles the tricyclic drugs. Mianserin produces few symptoms in overdose[60] and the fatal toxicity of mianserin when taken in overdose is very low.[35]

In addition, this drug is almost free of anticholinergic effects and produces less cardiac depression than the tricyclics.[61] Trazodone has been reported to possess lower membrane stabilizing activity than amitriptyline or imipramine[41] which may explain the relatively low number of deaths from overdose with this drug. [41]

Monamine Oxidase Inhibitors (MAOIs)

The lethality of older MAOIs does not arise from membrane stabilizing activity[41] and is not due to their ability to interact with substances such as tyramine to produce a hypertensive crisis (the 'cheese' reaction). Features of overdose have been well known for many years and described by Blackwell in 1981.[60] The MAOIs cause a gradual increase in muscle tone until the patient has severe spasms of all muscle groups, which can lead to excessive heat production and death from hyperthermia.[62] It is now apparent that these features represent a serotonergic syndrome and careful management can prevent a fatal outcome.[62] This may explain why the apparent overdose fatality has fallen over the years. Another explanation might be that numbers of prescriptions for the older MAOIs have fallen. The decrease in their popularity is likely to reduce the actual number of attempted and completed suicides using MAOIs and reduce the statistical significance of FTI values.

The newer generation drugs such as moclobemide which are reversible inhibitors of MAO cause a similar serotonergic syndrome to the older MAOIs in overdose. Although they may have lower overdose toxicity, it is too early to tell whether they have a lower Fatal Toxicity Index than their predecessors.

Appraisal of Evidence for Prevention, versus Aggravation, of Suicide by SSRIs; Comparison with Other Antidepressant Agents

The irony that patients may kill themselves with the drugs prescribed to treat their depression and its complications (which includes suicide) is especially great because one measure of their efficacy in clinical trials is their performance on the suicide item of the Hamilton rating scale for depression.

Almost every antidepressant has occasionally been associated with the intensification of suicidal ideation, or even the emergence of suicidal thoughts in the patient being treated. In the absence of accurate comparative data however, it is impossible to conclude whether the drug itself, or the disorder being treated, was at fault. One study which must be considered in this context is a large, placebo-controlled trial, lasting one year, of maprotiline.[17] In this study maprotiline administration was associated with significantly more suicide attempts than placebo ($P<0.03$). Of the 331 patients who were receiving placebo, only one committed suicide. However, among the 332 patients on maprotiline (75 mg/day), there were 4 attempted suicides and 3 successful suicides. Among the 329 patients on an intermediate dose of maprotiline (37.5 mg/day), there were 5 attempted suicides and 2 successful suicides. Given that both doses of maprotiline were shown to be significantly more effective in reducing the incidence of relapse than placebo, it is reasonable to assume that patients receiving active medication were compliant with treatment. The implication of this study is that maprotiline administration is associated with an increased incidence of suicide in spite of clinical effectiveness in relieving depression. A study of all deaths by suicide in Switzerland in 1990 found that maprotiline was the most commonly used drug.[63] Although this result tended to reflect prescribing habits, the difference between maprotiline and clomipramine in terms of prescription data was two-fold whereas the difference in the number of deaths associated with each agent was four-fold.

In a study which was based on prescription event monitoring, amitriptyline was associated with a higher incidence of overdose than the newer antidepressant, mianserin (15/1000 compared to 11/1000 for mianserin).[16] While Henry and Antao[31] calculated that this difference was statistically significant ($\chi^2 = 8.77$; $P<0.005$), the results are not conclusive, since the patient groups differed, with more chronic patients in the amitriptyline group than in the mianserin group.

The reasons for the possibility that the TCAs may be associated with an increase in suicide needs to be considered. One reason may lie in the dose used. TCAs need to be given in a dose of 125-150 mg to be effective,[64] otherwise there is the danger not only of failure to treat the patient but also of a slight increase in motivation without a reduction in hopelessness, making suicide more likely. A number of antidepressants impair cognitive and psychomotor performance; this could be a factor behind their apparent toxicity in overdose. However, there was no evidence of drug-induced cognitive toxicity in four patients in whom suicidal ideation was precipitated by desipramine, nortriptyline, amoxapine or trazodone.[65]

A report published in 1990 implicated the SSRI fluoxetine as a cause of suicidal behavior, on the grounds that six patients treated with the drug had violent, self-destructive thoughts.[66] Such behavior however may in fact have been influenced by a combination of factors, including: prior history of suicide attempts; concurrent treatment with several other drugs, including stimulants; and a tendency to alcohol abuse among some of the patients. The balance of opinion was that the patients' suicidal ideation was more likely to have arisen from their psychological disorder than from the drug used to treat it. A meta-analysis by Beasley et al[67] gave no indication that suicide was significantly more common during treatment with fluoxetine than with either TCAs or placebo. The pooled incidence of suicidal acts was 0.3% for fluoxetine, 0.2% for placebo and 0.4% for TCAs. In terms of emergence of suicidal thoughts, the pooled incidence was 1.2% for fluoxetine, 2.6% for placebo and 3.6% for TCAs. Statistical analysis showed that the incidence of emergent suicidal thoughts was significantly lower with fluoxetine than with placebo ($P = 0.042$) and TCAs ($P = 0.001$). In addition, a prescription monitoring study showed no difference in the incidence of suicide between patients treated with fluoxetine or another SSRI, fluvoxamine.[68]

Jick et al[69] have confirmed these findings, although their study of UK general practice databases suggested a particularly high suicide rate in people who took fluoxetine, compared to other antidepressants. However, once past history of suicide attempts and the number of antidepressants previously prescribed had been taken into account, there was no difference between any of the antidepressants. This supports the idea that SSRIs may be selectively prescribed for patients at greater risk of suicide in the first place; possibly a penalty of their reputation for early reduction of suicidal ideation and also of low toxicity in overdose.

There is some evidence to suggest that rather than provoking suicidal ideation, SSRIs may help to reduce it more rapidly than other antidepressants.[70] A meta-analysis by Montgomery et al[71] showed that paroxetine was significantly more effective than placebo in reducing suicidal thoughts, and that there were 5.6 times fewer suicides in paroxetine-treated patients than in those taking placebo, and 2.8 times fewer suicides than in patients receiving active medication. These findings are in keeping with the postulated link between reduced serotonergic neurotransmission and suicide. [45,71]

A study conducted in Sweden which investigated all cases of autopsy in which antidepressants were found in the blood and then related the data to sales of antidepressants, showed that lofepramine was rarely detected,[44] a finding which could be the result of selective prescribing or could indicate that lofepramine has an effect on suicidal ideation.

Conclusion

While the 300 deaths which occur from antidepressant overdose each year in Britain are small compared with the total number of suicides (approximately 6,000 each year), it should be noted that these deaths are largely preventable by prescribing less toxic alternatives. Although it can be argued that a failed suicide attempt may only delay the ultimate outcome, it is widely accepted that a suicide attempt is a poor predictor of future attempts;[21] about 10% of those who fail to kill themselves with acute overdose go on to successful suicide. Studies suggest that when a means of committing suicide becomes less available there is not,

as might be thought, a shift to another method. Many suicidal acts are impulsive and quickly regretted; a thwarted or failed attempt may never be followed by another attempt. Furthermore, a failed attempt by drug overdose might bring the patient under close medical supervision and lead to more effective treatment of their depression.

This chapter has considered several of the links between depression, suicide, 5-HT and the SSRIs. It is apparent that this class of drugs enjoys a special place in the therapeutic armamentarium, with, in addition to antidepressant effectiveness, evidence that they may reduce suicidal ideation. The tricyclic drugs on the other hand may be as effective or more effective in terms of antidepressant efficacy but may increase suicidal ideation. At the same time, the SSRIs have remarkably low toxicity in overdose which makes them especially safe for the depressed patient who is considered to be at risk of suicide.

References

1. Regier DA, Hirschfeld RMA, Goodwin FK et al. The NIMH depression awareness, recognition, and treatment program: structure, aims, and scientific basis. Am J Psychiatry 1988; 145:1351-1357.
2. Katon W, Roy-Byrne PP. Antidepressants in the medically ill: Diagnosis and treatment in primary care. Clin Chem 1988; 34:829-836.
3. Kind P, Sorensen J. The costs of depression. Int Clin Psychopharmacol 1993; 7:191-195.
4. Henry JA. Debits and credits in the management of depression. Br J Psychiatry 1993; 163 (Suppl 20):33-39.
5. Montgomery SA. Suicide and antidepressants. Drugs 1992; 43(Suppl):24-31.
6. Barraclough BM, Bunch J, Nelson B et al. A hundred cases of suicide: Clinical aspects. Br J Psychiatry 1986; 125:355-373.
7. Paykel ES. The treatment of depression: The relevance of research for clinical practice. Br J Psychiatry 1989; 155:754-763.
8. Levenson JL, Hamer RM, Rossiter LF. A randomized controlled study of psychiatric consultation guided by screening in general medical inpatients. Am J Psychiatry 1992; 149:631-637.
9. Kellerman AL, Rivara FP, Somes G et al. Suicide in the home in relation to gun ownership. New Engl J Med 1992; 327:467-472.
10. Office of Population Censuses and Surveys. Mortality statistics—accidents and violence (England and Wales), Series DH2. London: HMSO, 1990, 1991, 1992.
11. Diekstra RFW. The epidemiology of suicide and parasuicide. Acta Psychiatr Scand 1993; 371:9-20.
12. Walinder J, Carlsson P, Rutz W. The economic impact of an educational programme on diagnosis and treatment of depression in Sweden. In: Jonsson B, Rosenbaum J, eds. Health Economics of Depression—Perspectives in Depression, Vol 4. Chichester: John Wiley, 1993:97-110.
13. Teige B, Fleischer E. Medikament-og alkoholdodsfall undersokt ved Rettsmedisinsk institutt, Universitet I Oslo I arene 1977-1979. Tidsskr Nor Laegeforen 1981; 101:1563-1566.
14. Prescott LF, Highley MS. Drugs prescribed for self-poisoners. Br Med J 1985; 290:1633-1636.
15. Bulik CM, Carpenter LL, Kupfer DJ et al. Features associated with suicide attempts in recurrent major depression. J Affect Disord 1990; 18:29-37.
16. Inman WHW. Blood disorders and suicide in patients taking mianserin or amitriptyline. Lancet 1988; ii:90-92.
17. Rouillon R, Philips R, Serrurier D et al. Rechutes du depression unipolaire et efficacite de la maprotiline. L'Encephale 1993; XV:527-534.
18. Montgomery SA, Pinder RM. Do some antidepressants promote suicide? Psychopharmacology 1987; 92:265-266.
19. Goldstein RB, Black DW, Nasrallah A et al. The prediction of suicide: Sensitivity, specificity, and predictive value of a multivariate model applied to suicide among 1906 patients with affective disorders. Arch Gen Psychiatry 1991; 48:418-422.

20. Hawton K. Assessment of suicide risk. Br J Psychiatry 1987; 150:145-153.
21. Kreitman N. How useful is the prediction of suicide following parasuicide? In: Wilmotte J, Mendlewicz J, eds. New Trends in Suicide Prevention. Basel: Karger, 1982.
22. Motto JA. An integrated approach to estimating suicide risk. Suicide and life threatening behaviour 1991; 21:74-89.
23. Angst J, Stassen HH, Gross G et al. Suicide in affective and schizoaffective disorders. In: Marneros A, Tsuang MT, eds. Affective and Schizoaffective Disorders. Berlin; Springer Verlag, 1990:186-195.
24. Guze SB, Robins E. Suicide and primary affective disorders. Am J Psychiatry 1970; 117: 437-438.
25. Winokur G, Tsuang M. The Iowa 500: Suicide in mania, depression, and schizophrenia. Am J Psychiatry 1975; 132:650-653.
26. Callaham M, Kassel D. Epidemiology of fatal tricyclic antidepressant ingestion: Implications for management. Ann Emerg Med 1985; 14:1-9.
27. Diekstra RF. Suicide and attempted suicide: An international perspective. Acta Psychiatr Scand 1989; 354(Suppl):1-24.
28. Anon. Selective serotonin reuptake inhibitors for depression? Drug and Therapeutics Bulletin 1993; 31:57-58.
29. Henry JA. Serotonin syndrome. Lancet 1994; 343:607.
30. Riddle MA, Brown N, Dzubinski D et al Fluoxetine overdose in an adolescent. J Am Acad Child Adolesc Psychiatry 1989; 28:587-588.
31. Henry JA, Antao CA. Suicide and fatal antidepressant poisoning, Eur J Med 1992; 6:343-348.
32. Stanley M, Virgilio J, Gershon S. Tritriated imipramine binding sites are decreased in frontal cortex of suicides. Science 1982; 216:1337-1339.
33. Asberg M, Traskman L, Thoren P. 5-HIAA in cerebrospinal fluid-a biochemical suicide predictor? Arch Gen Psychiatry 1976; 33:1993-1997.
34. Asberg M, Schalling D, Traskman L et al. Psychobiology of suicide, impulsivity, and related phenomena. In Meltzer HY, ed. Psychopharmacology: The Third Generation of Progress. New York; Raven Press, 1987:655-668.
35. Henry JA, Alexander CA, Sener EK. Relative mortality from overdose of antidepressants. Br Med J 1995; 310:221-224.
36. Bolster M, Curran J, Busuttil. A five year review of fatal self-ingested overdoses involving amitriptyline in Edinburgh 1983-87. Hum Exp Toxicol 1994; 13:29-31.
37. Farmer RDT, Pinder RM. Why do fatal overdose rates vary between antidepressants? Acta Psychiatr Scand 1989; 80(Suppl 354):25-35.
38. Girdwood RH. Death after taking medicaments. Br Med J 1974; 1:501-504.
39. Barraclough BM. Are there safer hypnotics than barbiturates? Lancet 1974; i:57-58.
40. King LA, Moffat AC, King LA. Quantitative structure-activity relationships in forensic toxicology. In: Dearden JC ed. Quantitative Approaches to Drug Design. Oxford: Elsevier, 1983:277-278.
41. Cassidy S, Henry J, Fatal toxicity of antidepressant drugs in overdose. Br Med J 1987; 295:1021-1024.
42. Retterstøl N. Norwegian data on death due to overdose of antidepressants. Acta Psychiatr Scand 1989; 80(Suppl 354):61-68.
43. Vuori E, Klaukka T, Lahti T. Fatal poisonings with antidepressants in Finland 1985-1987. Acta Psychiatr Scand 1989; 80(Suppl 354):55-60.
44. Malmvik J, Löwenhielm CGP, Melander A. Antidepressants in suicide: Differences in fatality and drug utilisation. Eur J Clin Pharmacol 1994; 46:291-294.
45. Kapur S, Mieczkowski T, Mann J. Antidepressant medications and the relative risk of suicide attempt and suicide. JAMA 1992; 268:3441-3445.
46. Molcho A, Stanley M. Antidepressants and suicide risk: Issues of chemical and behavioural toxicity. J Clin Psychopharmacol 1992; 12:13S-18S.
47. Kelvin AS, Hakansson S. Comparative acute toxicity of paroxetine and other antidepressants. Acta Psychiatr Scand 1989; 80:31-33.
48. Dziukas LJ, Vohra J. Tricyclic antidepressant poisoning. Med J Aust 1991; 154:344-350.

49. Borys DJ, Setzer SC, Ling LT et al. The effects of fluoxetine in the overdose patient. Clin Toxicol 1990; 28:331-40.
50. Banahan BF, Shelkun PH. Tricyclic antidepressant overdose: Conservative management in a community hospital with cost saving implications. J Emerg Med 1990; 8:451A.
51. Frommer DA, Kulig KW, Marx JA et al. Tricyclic antidepressant overdose. A review. JAMA 1987; 257:521-526.
52. Pentel PR, Benowitz NL. Tricyclic antidepressant poisoning. Med Toxicol 1986; 1:101-121.
53. Callaham M, Kassel D. Epidemiology of fatal tricyclic antidepressant ingestion: Implications for management. Ann Emerg Med 1985; 14:1-9.
54. McGrady H, Rees JA. Toxicity of dothiepin in overdose. Lancet 1994; 343:292.
55. Buckley NA, Dawson AH, Whyte IM et al. Toxicity of dothiepin in overdose. Lancet 1994; 343:735.
56. Crome P, Ali P. Clinical features and management of self-poisoning with newer antidepressants. Med Toxicol 1986; 1:411-420.
57. Wedin GP, Oderda GM, Klein-Schwartz W et al. Relative toxicity of cyclic antidepressants. Ann Emerg Med 1986; 15:797-804.
58. Lundstrom M, Eriksson A, Thorson J et al. Fatal overdose with citalopram. Lancet 1996; 348:339-340.
59. Brion F, Brion N, Durigon M. Fatal overdose with citalopram? Lancet 1996; 348:1380.
60. Blackwell B. Adverse effects of antidepressant drugs. Drugs 1981; 21:273-282.
61. Wakeling A. Efficacy and side effects of mianserin, a tetracyclic antidepressant. Postgrad Med J 1983; 59:229-231.
62. Amrein R, Allen SR, Vranesic D et al. Antidepressant drug therapy: Associated risks. J Neural Trans 1988; 26:73-86.
63. Michel K, Arestegui G, Spuhler T. Suicide with psychotropic drugs in Switzerland. Pharmacopsychiatr. 1994; 27:114-118.
64. Paykel ES, Priest RG. Recognition and management of depression in general practice: Consensus statement. Br Med J 1992; 305:1198-1202.
65. Damluji NF, Ferguson JM. Paradoxical worsening of depressive symptomatology caused by antidepressants. J Clin Psychopharm 1988; 8:347-349.
66. Teicher MH, Glod C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. Am J Psychiatry 1990; 147:207-210.
67. Beasley CM, Dornseif BE, Bosomworth JC et al. Fluoxetine and suicide: A meta-analysis of controlled trials of treatment for depression. Br Med J 1991; 303: 685-692.
68. Edwards JG, Inman WHW, Wilton L et al. Prescription-event monitoring of 10401 patients treated with fluvoxamine. Br J Psychiatry 1994; 164:387-395.
69. Jick SS, Dean AD, Jick H. Antidepressants and suicide. Br Med J 310; 1995:215-218.
70. Wakelin JS. The role of serotonin in depression and suicide: Do serotonin reuptake inhibitors hold the key? Adv Biol Psychiatry 1988; 17:70-83.
71. Montgomery SA, Dunner DL, Dunbar GC. Reduction of suicidal thoughts with paroxetine in comparison with reference antidepressants and placebo. Eur J Neuropsychopharmacol 1995; 5:5-13.
72. Malmuik J, Löwenhielm CGP, Melander A. Antidepressants in suicide: Differences in fatality and drug utilization. Eur J Clin Pharmacol 1994; 46:291-294.

CHAPTER 8

Mechanism of Action of Different Classes of Antidepressants: Evidence from 5-HT Challenge Studies

Ian M. Anderson and Christopher Mortimore

The discovery in the 1950s that imipramine and iproniazid had antidepressant properties was soon followed by the recognition that they acted on monoamine systems. This laid the foundation for two interrelated but logically distinct theories which have dominated biological research into depression and its treatment ever since:

1. the hypothesis that monoamine function is abnormal in depression and
2. the hypothesis that altering monoamine function can treat the depressed state.

The second hypothesis suggests that changes in monoamine function are sufficient, or possibly even necessary, to alleviate depression and, by extension, implies that a common mechanism could underlie the action of all antidepressant drugs in spite of differences in their acute pharmacology. In this chapter we will explore an aspect of the second hypothesis by reviewing human data investigating the effect of antidepressants on serotonin (5-hydroxytryptamine, 5-HT) function using neuroendocrine challenge tests.

Preclinical Background

The detailed pharmacology of a drug or class of drugs can be studied in animals and the findings extrapolated to humans. However species differences necessitate caution, e.g., the absolute and relative affinity of antidepressants for the human monoamine transporter is not identical to that seen in rats.[1] Any attempt to relate pharmacology to clinical efficacy must eventually be tested in humans with psychiatric conditions. The investigation of pharmacological endpoints of antidepressant action by measuring the effect of chronic administration of these compounds on receptor number and function in animals has revealed a few more or less consistent changes, particularly downregulation of β-adrenoceptors and 5-HT_2 receptors in the cerebral cortex.[2] However it has become apparent that many newer antidepressants including selective serotonin reuptake inhibitors (SSRIs) have less consistent effects on receptor numbers[3] suggesting that effects downstream from the receptor may be equally or more important.

Models using functional endpoints ranging from neuronal firing to behavior have allowed exploration of receptor function in a dynamic manner. The influential 5-HT_{1A}-enhancement model proposed by Blier and de Montigny (see refs. 4,5), based on electrophysiological experiments in animals, is of particular relevance to the human studies described in this chapter. They proposed that antidepressants act by increasing neurotransmission through postsynaptic 5-HT_{1A} receptors in the hippocampus, a view consistent with the suggested

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role of hippocampal 5-HT_{1A} pathways in mediating resilience to adversity.[6] Drugs with different pharmacodynamic properties are believed to enhance 5-HT_{1A} receptor-mediated neurotransmission in a variety of ways: tricyclic antidepressants (TCAs) by increasing postsynaptic 5-HT_{1A} receptor sensitivity, SSRIs by increasing 5-HT release secondary to desensitization of 5-HT neuronal cell body (5-HT_{1A}) and terminal (5-$HT_{1B/1D}$) autoreceptors in the face of continuing reuptake inhibition, and monoamine oxidase inhibitors (MAOIs) by increased 5-HT neuronal firing due to desensitization of 5-HT_{1A} autoreceptors on the cell bodies and α_2 heteroreceptors in the terminal field in the context of reduced neurotransmitter breakdown.

Recent microdialysis studies have confirmed that chronic SSRI treatment increases neuronal release of 5-HT.[7] However investigations of the effects of chronic antidepressants on 5-HT_{1A}-mediated behavioral and hormonal responses and 5-HT_{1A} receptor sensitivity in animals give conflicting results.[8-13] The use of pharmacological challenge tests in humans allows investigation of the functioning of monamine pathways in healthy volunteers and subjects with psychiatric disorders by measuring a physiological endpoint, usually hormonal, but other measures are also possible such as body temperature, psychological state or cerebral blood flow.[14]

5-HT Challenge Tests in Humans

Table 8.1 summarizes the hormonal responses to, and the putative receptor mediation of, 5-HT drugs used in human pharmacological challenge tests to investigate the effects of antidepressants on 5-HT function. As will be seen from the data presented below, characterization is patchy and relies in many cases on single studies (albeit backed up by animal data) so that the receptor mediation must be taken as provisional. A broad categorization of the challenges into those acting presynaptically (precursors, uptake inhibitors/releasers) and postsynaptically (agonists) can be made although as discussed below the distinction is often less certain than it at first appears. With regard to particular 5-HT pathways, the challenges can be principally divided into those believed to act via 5-HT_{1A} receptors or 5-HT_2 receptors.

5-HT Precursor Challenge

The best characterized precursor challenge is intravenous administration of the amino acid, *l*-tryptophan (TRP), which reliably stimulates prolactin (PRL) and growth hormone (GH) secretion. Both responses are enhanced by acute 5-HT reuptake blockade with clomipramine[15] although only the PRL response is inhibited by the non-selective 5-HT receptor antagonist, metergoline.[16] However both responses are inhibited by pindolol which has 5-HT_{1A} receptor antagonist properties.[17] Neither response is blocked by the 5-$HT_{2A/2C}$ receptor antagonists, ritanserin and ketanserin,[18,19] or by granisetron, a 5-HT_3 receptor antagonist.[20] These data suggest that the hormonal responses are mediated by 5-HT_{1A} receptors although there is less certainty about the GH than the PRL response.

5-Hydroxytryptophan (5-HTP) is the immediate precursor of 5-HT. Parenteral administration results in unacceptable side-effects so it is generally given orally and, probably because of this, hormone responses tend to be unreliable. An interesting difference from TRP challenge is the stimulation of cortisol secretion. Animal studies suggest 5-HT_2 receptor-mediation of hormonal responses.[21] In humans the GH response is antagonized by cyproheptidine, a more potent 5-HT_2 than 5-HT_1 receptor antagonist[22] while the cortisol response is antagonized by ritanserin in one study[23] but not another.[24] Pindolol lacks effect on the cortisol response,[25] but PRL stimulation appears to be antagonized by both ritanserin[23] and pindolol.[25] Therefore the mediation of 5-HTP-induced hormone responses in humans are not entirely certain although the involvement of 5-HT_2 receptors seems most

Table 8.1. 5-HT drugs used in human pharmacological challenge tests: Hormonal responses and putative receptor mediation

Drug	5-HT action	Hormone (putative receptor mediation)		
		Prolactin	Growth hormone	ACTH/cortisol
5-HTP*	precursor	(↑) (5-HT_2/ 5-HT_{1A}	(↑) (5-HT_2)	(↑) (?5-HT_2)
Tryptophan	precursor	↑ (5-HT_{1A}) ↑ (?)	↑ (5-HT_{1A})	(↑)
Clomipramine	reuptake inhibitor	↑ (?)	-	↑ (?)
Fenfluramine	reuptake inhibitor/releaser	↑ (5-HT_2)	-	↑ (5-HT_2)
Buspirone	5-HT_{1A} agonist	↑ (D_2/5-HT_{1A})	↑ (5-HT_{1A})	↑ (5-HT_{1A})
Ipsapirone	5-HT_{1A} agonist	(↑) (5-HT_{1A})	↑ (5-HT_{1A})	↑ (5-HT_{1A})
Gepirone	5-HT_{1A} agonist	↑ (5-HT1A)	↑ (5-HT_{1A})	↑ (5-HT_{1A})
Sumatriptan	5-HT_{1D} agonist	(↓)(5-HT_{1D})	↑ (5-HT_{1D})	-
mCPP	5-HT_{2C} agonist ?5-HT releaser	↑ (5-HT_{2C})	↑ (?)**	↑ (5-HT_{2C})
MK-212	5-HT_{1A}/5-HT_{2C} agonist	↑ (5-HT_{1A}/ 5-HT_2)	-	↑ (5-HT_2)

↑ , increase in plasma hormone; (↑), weak/inconsistent increase in plasma hormone; (↓), inconsistent decrease in plasma hormone; -, no response; *, oral administration; **, increases GH after intravenous but not oral administration.

likely and there may be a 5-HT_{1A}/5HT_2 receptor interaction involved in the PRL response. It is unclear why TRP and 5-HTP apparently probe different 5-HT receptors.

5-HT Reuptake Inhibitor/Releaser Challenge

Fenfluramine, either as a racemic (*d,l*) mixture, or the dextro (*d*) isomer, has been widely used as a 5-HT challenge although its future use is in question following its withdrawal due to potential cardiac problems.[26] In spite of some concerns about the 5-HT-specificity of *d,l*-fenfluramine, responses to both formulations of fenfluramine appear qualitatively similar.[27] *d*-Fenfluramine affects 5-HT neurotransmission in a number of ways. It is a 5-HT-releasing agent, a process requiring uptake via the 5-HT transporter, it blocks 5-HT reuptake and its metabolite *d*-norfenfluramine is believed to stimulate postsynaptic 5-HT_{2C}

receptors.[28] Administration to humans stimulates PRL and ACTH/cortisol secretion. However, the widely held belief that hormonal responses are due to its 5-HT releasing action is difficult to reconcile with the persistence (sometimes increase) of responses after administration of drugs which block 5-HT reuptake, such as clomipramine, imipramine, amitriptyline, fluoxetine and fluvoxamine.[29-32] Hormonal responses to fenfluramine may therefore be due to either 5-HT release independent of active 5-HT reuptake or due to direct postsynaptic receptor stimulation. Whatever the precise mechanism, antagonist studies suggest that the PRL response to fenfluramine is mediated by postsynaptic 5-HT_2 receptors as they are antagonized by the 5-$HT_{2A/2C}$ receptor antagonists, ritanserin[33] and amesergide,[34] but not by pindolol[35] or the 5-HT_3 antagonist, ondansetron.[36] The cortisol response to fenfluramine tends to be less robust; it is often not reported and the 5-HT receptors involved have been less well characterized. However, clozapine, which has 5-HT_2 antagonist properties, has been shown to attenuate both PRL and cortisol responses to *d*-fenfluramine in schizophrenic patients.[37]

Clomipramine given intravenously stimulates PRL and cortisol secretion. Its metabolite, desmethylclomipramine, is a potent noradrenaline reuptake inhibitor but is not detectable during acute clomipramine challenge.[38] The 5-HT receptor pathways have not been characterized as to our knowledge no antagonist studies have been carried out. Although hormonal responses are likely to be a consequence of increased synaptic 5-HT concentrations the contribution of alternative non-specific mechanisms such as a stress reaction to nausea are possible.[39]

5-HT_1 Receptor Agonist Challenge

The azapirones (buspirone, ipsapirone, gepirone) are partial 5-HT_{1A} receptor agonists that stimulate PRL, GH and cortisol secretion and lower body temperature.[40] 5-HT_{1A} receptors are sited both presynaptically (cell body autoreceptors) and postsynaptically[41-44] so that responses to challenge by these compounds could reflect pre- and/or postsynaptic receptor stimulation. Pindolol has been shown to antagonize the GH response to buspirone, the cortisol response to ipsapirone and the hypothermic responses to buspirone and ipsapirone[45-47] suggesting that these are mediated by 5-HT_{1A} receptors. The PRL response to buspirone is particularly robust but the weight of evidence suggests that this is mediated by blockade of dopaminergic (D_2) receptors,[48] in particular the failure of pindol to antagonize the response in the same study where GH and hypothermic responses were blocked.[45] The GH and cortisol responses are likely to reflect postsynaptic activation but there is controversy as to whether the hypothermic response is presynaptic or postsynaptic. In the mouse, presynaptic mediation of 5-HT_{1A} receptor-induced hypothermia is suggested by its attenuation following inhibition of 5-HT synthesis using *p*-chlorophenylalanine and 5-HT neuronal destruction using 5,7-dihydroxytryptamine[49,50] but similar lesions in the rat have produced conflicting results[51,52] as have results using raphé micro-injection of 5-HT_{1A} receptor agonists.[53,54] In a preliminary report in humans, reducing presynaptic 5-HT function using acute tryptophan depletion failed to affect the hypothermic response to buspirone[55] consistent with a postsynaptic mechanism; however a single small negative study such as this is not definitive.

Sumatriptan is a 5-HT_{1D} receptor agonist which increases plasma GH with a variable effect in decreasing plasma PRL.[56-59] Cyproheptadine antagonizes the GH response suggesting 5-HT involvement but this agent is a non-selective 5-HT receptor antagonist with uncertain effects at 5-HT_{1D} receptors.[56] However the finding that another 5-HT_{1D} receptor agonist, rizatriptan, also elevates GH[59] is suggestive of 5-HT_{1D} mediation of the response. 5-HT_{1D} receptors act as terminal autoreceptors on 5-HT neurons and also occur on postsynaptic sites.[60] If the reduction in plasma PRL concentration is a real effect of

sumatriptan it is likely to reflect a presynaptic action but the site of the receptor mediating the GH response is unknown.

5-HT$_2$ Receptor Agonist Challenge

m-Chlorophenylpiperazine (*m*CPP) is an increasingly widely used 5-HT challenge which increases body temperature, stimulates PRL and ACTH/cortisol secretion and causes anxiety with GH stimulation occurring after intravenous but not oral administration.[61,62] It is non-selective in its binding to 5-HT receptors,[63,64] but animal studies suggest that many of its agonist effects are mediated by 5-HT$_{2C}$ receptors.[65] *m*CPP's postsynaptic site of action has been challenged in animals by an in vivo microdialysis finding that it releases 5-HT and that the 5-HT reuptake inhibitor, fluoxetine, blocks this effect and partially attenuates *m*CPP-mediated PRL release.[66] There are however contradictory reports about *m*CPP's affinity for the human brain 5-HT transporter,[64,67] possibly related to different methodologies. In humans, the PRL, cortisol and anxiety responses are antagonized by non-selective 5-HT antagonists[68,69] and by ritanserin[70] as well as clozapine,[71,72] but not by the 5-HT$_3$ antagonist, endo-*N*-(8-methyl-8-azabicyclo[3.2.1]oct-3yl)-2,3-dihydro-3,3-dimethyl-indole-1-carboxamide HCl (BRL 46470).[73] However, ondansetron is reported to attenuate cortisol and behavioral responses without affecting the PRL response in another study[74] raising the possibility that 5-HT$_3$ receptors may be involved in some responses. GH stimulation is not blocked by ritanserin[70] raising doubts about the role of 5-HT$_2$ receptors in this response. In summary the situation with regard to *m*CPP-mediated responses is complex with the strongest evidence linking PRL, cortisol and behavioral responses with 5HT$_2$ receptors. Animal evidence further suggests that it is the 5-HT$_{2C}$ receptor subtype that is involved. However the assumption that responses purely reflect postsynaptic receptor function must be treated with caution.

6-Chloro-2-(l-piperazinyl)pyrazine (MK-212) binds to a variety of 5-HT receptors including 5-HT$_{2A}$, 5-HT$_{2C}$ and 5-HT$_{1A}$ receptors.[63] Animal studies show dose-related stimulation of PRL and ACTH/cortisol with antagonism by 5-HT$_{2A/2C}$, but not 5-HT$_{1A}$ receptor antagonists.[75-77] It stimulates PRL and cortisol secretion after oral administration in humans[75,78] with pindolol pretreatment partially antagonizing PRL but not cortisol responses.[79] Overall therefore the evidence is supportive of 5-HT$_{2A/2C}$ mediation of cortisol stimulation in humans with less certainty about the PRL response (reminiscent of 5-HTP, see above).

Effect of Antidepressant Treatment on Responses to 5-HT Challenge Tests

Studies of the effect of antidepressants on 5-HT challenge tests have been carried out in volunteers and patients with depressive disorder and obsessive-compulsive disorder (OCD). Normal volunteer studies avoid the possible confound of alteration in state-dependent 5-HT abnormalities that have been described in both depressive disorder[14] and OCD.[80,81] It is also possible that effects in depressed and non-depressed subjects might differ (e.g., ref. 82). Studies in both different patient groups and healthy volunteers therefore provide complimentary information.

Tricyclic Antidepressants (TCAs)

Although TCAs are traditionally considered as a group, individual drugs differ in important properties and receptor binding profiles. Clomipramine and, to a lesser extent, amitriptyline and imipramine have greater 5-HT reuptake inhibiting properties than other TCAs. Sedative and non-sedative TCAs differ in H$_1$ receptor antagonism and 5-HT$_2$ receptor

antagonism varies between drugs.[83] The property most shared is their ability to inhibit noradrenaline reuptake.[83]

TRP challenge generally reveals a consistent picture of enhanced PRL responses by TCAs. This is seen in normal volunteers with acute clomipramine[15] and chronic desipramine.[84] In depressed patients similar findings occur with desipramine[85,86] and amitriptyline.[85,87] In the study using amitriptyline by Cowen et al[87] this effect was only evident if three patients with pretreatment weight loss were excluded, probably because weight loss is itself associated with increased PRL responses to TRP in women.[88] The enhancement with clomipramine occurs acutely (presumably related to acute 5-HT reuptake inhibition; see also: SSRIs, below) whereas chronic treatment is required with desipramine[86] suggesting that a different mechanism is involved (possibly pre- or postsynaptic 5-HT_{1A} receptor changes, but see below). The increase in PRL responses is not related to clinical response.[85-87] Changes in GH responses after TCAs have been less consistent (where reported) with increases seen with acute clomipramine[15] but not with chronic amitriptyline[87] or desipramine.[84]

These results suggest that 5-HT_{1A} receptor-mediated neurotransmission may be enhanced by TCAs, at least in some pathways, and that this is not just a consequence of 5-HT reuptake inhibition (which is unlikely by itself to account for antidepressant effects given the time lag in onset of antidepressant action). A possible mechanism for this, as suggested by the 5-HT_{1A} enhancement model, is increased postsynaptic 5-HT_{1A} receptor sensitivity but studies with 5-HT_{1A} receptor agonists do not support this:

1. a normal volunteer study with lofepramine found no alteration in the GH (or PRL) response to buspirone[89] and
2. Lesch et al[90] report no alteration in the ACTH/cortisol response to ipsapirone in depressed patients treated with amitriptyline.

An alternative explanation is increased serotonergic neuronal firing due to the desensitization of 5-HT_{1A} autoreceptors and studies using the hypothermic response to azapirones, a possible index of presynaptic 5-HT_{1A} receptor function (but see page 116), provide some support for this in that amitriptyline causes blunted hypothermic response to ipsapirone[90] and buspirone.[91] However, desensitization of 5-HT_{1A} autoreceptors (also seen with the SSRIs, see page 119) is not found with lofepramine, a selective noradrenaline reuptake inhibitor, as measured by buspirone-induced hypothermia in one volunteer study[89] suggesting that 5-HT_{1A} autoreceptor desensitization may depend on 5-HT reuptake inhibition and that noradrenaline reuptake inhibitors increase presynaptic 5-HT neuronal function by a different mechanism. One way this could occur is through sensitization of 5-HT cell body α_1-adrenoceptors or desensitization of terminal α_2-heteroreceptors.[41,92-95] This would result in increased 5-HT neuronal firing or terminal release of 5-HT and is consistent with the observation that TCA treatment results in blunted GH responses to the α_2-adrenoceptor agonist, clonidine.[96]

With regard to the effect of TCAs on putative 5-HT_2-mediated responses to presynaptic pharmacological challenge, Meltzer[97] reports that three to six weeks treatment of 14 patients with depressive illness or OCD with a mixed group of TCAs (including 1 patient on maprotiline) has no effect on the cortisol response to 5-HTP. Studies using fenfluramine challenge give inconsistent findings in depressed patients with enhanced PRL responses following treatment with clomipramine, imipramine and amitriptyline[29-31] but non-significantly lower responses to a mixed group of antidepressants (mostly TCAs) in another a study.[98] In studies using the more noradrenaline-specific reuptake inhibitors, nortriptyline and maprotiline, decreased PRL responses are reported[98,99] although only the study with nortriptyline reached statistical significance, and then at five, but not three, weeks treatment. One possible interpretation is that TCAs with 5-HT reuptake properties result in

enhanced 5-HT_2-mediated function but noradrenaline-specific drugs are associated with reduced function. Caution is needed in the interpretation of these results because of the potential confound of alterations in mood state and the lack of studies using healthy volunteers, e.g., in the study by O'Keane et al[31] the PRL responses are reported to 'normalize' and there is no effect of treatment on cortisol responses. This is consistent with the study by Leatherman et al[100] reporting that clomipramine-induced PRL responses increase after mixed antidepressant treatment in responders, but not non-responders, suggesting a state-dependent rather than pharmacological explanation. There are few data on the effects of TCAs on putative 5-HT_2-mediated responses to postsynaptic pharmacological challenge; surprisingly there appear to be no studies using *m*CPP and only one study using MK-212[97] which reports no alteration in cortisol responses after three to six weeks treatment of nine patients with depressive disorder or OCD using an unspecified range of TCAs.

In summary:

1. TCAs appear to enhance 5-HT_{1A} neurotransmission by an action on the presynaptic 5-HT neuron without altering postsynaptic 5-HT_{1A} receptor sensitivity.
2. TCAs, with and without 5-HT reuptake inhibitor properties, may enhance 5-HT_{1A} neurotransmission by different mechanisms. This suggestion however rests on the findings of one study.[89]
3. Effects on 5-HT_2 receptor pathways are somewhat conflicting and potentially confounded by changes in illness condition. While no consistent overall effects emerge, it is possible that noradrenaline-specific TCAs decrease 5-HT_2 function while those with 5-HT reuptake inhibition result in enhanced function.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Consistent with the findings described above with TCAs, treatment of depressed patients with the SSRI, fluvoxamine, results in increased PRL responses to TRP present at one week and to an even greater extent at four weeks.[86] Probing of 5-HT_{1A} receptor function using ipsapirone, buspirone and gepirone following chronic SSRI treatment gives a consistent picture of blunted cortisol, GH, psychological and hypothermic responses in healthy volunteers and patients with OCD[14,101,102] suggesting both pre- and postsynaptic 5-HT_{1A} receptors are desensitized. The blunted GH and psychological responses to buspirone are seen in spite of a three-fold increase in plasma buspirone concentrations.[102] These findings are not easily reconciled, but one interpretation is that the balance of effects is enhancement of net 5-HT_{1A} neurotransmission in spite of postsynaptic receptor desensitization.

A further presynaptic mechanism of potential importance is the effect of SSRIs on 5-HT_{1D} receptor function. One study reports no effect of paroxetine on PRL suppression following sumatriptan[103] and neither is a significant decrease in GH response seen (PJ Cowen personal communication) suggesting that SSRIs do not desensitize 5-HT_{1D} receptors.

Studies using presynaptic 5-HT_2 receptor probes to investigate the effects of SSRIs have not produced entirely consistent findings and are difficult to interpret. The 5-HTP-induced cortisol response, investigated in depressed and OCD patients after 4-12 weeks of treatment with fluoxetine[97] and 8 weeks with paroxetine,[82] shows an increase. A more complex finding is reported after paroxetine in healthy volunteers with marked enhancement at 1 week which is nearly back to baseline at 3 weeks.[82] A reduction in plasma 5-HTP concentration following paroxetine in controls but not patients offers a pharmacokinetic explanation of this finding although it is possible that the effect of SSRIs on depressed subjects and volunteers are not the same. Studies with *d*-fenfluramine in depressed patients treated with fluoxetine[31] and OCD patients treated with fluvoxamine[32] show increased PRL responses following treatment but in both cases the responses appear to 'normalize' rather than show enhancement compared to controls. In contrast Kasper et al[98]

report non-significantly blunted PRL responses to *d,l*-fenfluramine in depressed patients following treatment with fluvoxamine. The cortisol response to *d*-fenfluramine is reportedly unaltered by fluoxetine treatment.[31] Although no relationship is seen between clinical response and degree of PRL enhancement in the *d*-fenfluramine studies, as discussed above, it is possible that improvement in the depressed state may at least partly account for these findings.

Results from postsynaptic 5-HT_2 receptor probes are inconclusive. Hollander et al[104] reports enhanced PRL and cortisol responses to *m*CPP in OCD patients treated with fluoxetine but plasma *m*CPP concentrations are increased by the SSRI making interpretation difficult. In contrast Quested et al[105] report a blunting of PRL and temperature responses to intravenous *m*CPP in normal volunteers treated for three weeks with paroxetine. Fluoxetine is reported to enhance cortisol responses to MK-212 in depressed patients[97] but no pharmacokinetic data are given.

In summary:

1. In common with TCAs, from the evidence of studies using TRP, SSRIs appear to enhance net neurotransmission through 5-HT_{1A} receptor-mediated pathways.
2. The primary mechanism for this action is probably desensitization of presynaptic 5-HT_{1A} receptors but there is also evidence that SSRIs induce desensitization of postsynaptic 5-HT_{1A} receptors, a property not so far reported for TCAs. It is difficult to fully reconcile this with the overall enhancement suggested by the TRP studies.
3. There is less clarity regarding effects of SSRIs on 5-HT_2 receptor-mediated pathways; enhanced neurotransmission is suggested by the studies using 5-HTP but not consistently with fenfluramine or post-synaptic 5-HT_2 receptor probes.

Other Antidepressants

Monoamine oxidase inhibitors (MAOIs) increase the PRL response to TRP[106] and the cortisol response to 5-HTP[107] in depressed patients suggesting they may increase 5-HT_{1A}/5-HT_2 receptor function but more specific challenge data are unavailable. Antidepressants which lack both 5-HT and noradrenaline reuptake inhibition such as mianserin and trazodone do not enhance the PRL response to TRP[108,109] indicating that this is not a universal property of antidepressant drugs. Nefazodone, related to trazodone and with a similar pharmacology, increases PRL concentrations and temperature when given acutely, an action attributed to its metabolite *m*CPP.[110] Chronic treatment with nefazodone results in decreased responses to acute nefazodone challenge suggesting decreased 5-HT_{2C} receptor sensitivity[111] which is similar to the blunted responses to *m*CPP challenge seen following repeated *m*CPP administration.[112]

Lithium has antidepressant properties and has been investigated in a number of studies. PRL responses to intravenous TRP are increased following acute and chronic treatment in normal volunteers[113,114] although no effect is seen on GH. This is a specific effect on 5-HT-mediated PRL release as PRL responses to dopamine blockade are not altered by lithium treatment.[113] In depressed patients an acute enhancement of the PRL response returns to baseline after three weeks of lithium treatment in one study[115] but sustained enhancement is seen in another in treatment-resistant patients on antidepressants,[116] correlating with clinical response in those who improved but not in non-responders. Lithium treatment also produces a non-significant increase in the PRL response to another presynaptic 5-HT challenge, clomipramine,[117] although the receptors mediating the response are not known. On balance this indicates enhanced function of 5-HT_{1A}receptor-mediated pathways. However, lithium does not alter 5-HT_{1A} receptor sensitivity as measured by PRL, GH, cortisol and temperature responses to gepirone after 7 days treatment in normal volunteers[118] indicating a presynaptic mechanism independent of any alteration

in 5-HT_{1A} autoreceptor function. Lithium might be expected to reduce 5-HT_2 receptor function because of its inhibitory effects on the phosphatidyl inositol second messenger system linked to 5-HT_2 receptors.[119] However, lithium treatment is reported both to enhance the cortisol response to 5-HTP in depressed patients[107] and to have no effect, or a trend to reducing, the PRL response to *d*-fenfluramine in normal volunteers[120] and depressed patients on clomipramine[30] leaving open its overall effect on 5-HT_2 function.

Conclusion

Caution is required in interpreting the results available from challenge studies for a number of reasons. First, the specificity of each challenge is open to question, both because the drugs themselves are not selective and because in many cases the responses have not been characterized with appropriate antagonists. Secondly, the endpoint being used to assess 5-HT pathway function may be affected by factors other than the antidepressant drug treatment: for example, a change in the psychiatric state of the patient, weight changes etc. Indeed it is not certain that responses are affected in the same way in patients and controls and that is apparent in some studies discussed. Thirdly, the challenge tests are believed to probe hypothalamic 5-HT function and there is evidence that antidepressants may have different effects in different brain regions.[121] While the hypothalamus is likely to be important in certain aspects of depression (i.e., autonomic and endocrine abnormalities), changes there may not reflect the action of antidepressants in other important areas such as the hippocampus.

Given those caveats there are a number of interesting findings that provide information about the mechanism of action of antidepressants in human subjects and reveal similarities and differences between classes of antidepressant drugs. These are summarized in Table 8.2. The 5-HT_{1A} receptor-enhancement theory derived from animal experiments is only supported in a general way with important differences in detail. The main conclusions we draw from the data are that:

1. Antidepressants do alter 5-HT function.
2. No effect on 5-HT function appears necessary for antidepressant action, i.e., there are likely to be a number of different mechanisms that achieve the same end. However, enhancement of neurotransmission through 5-HT_{1A} receptor pathways revealed by presynaptic challenge with TRP is common to most (but not all) antidepressants. This is largely in agreement with the 5-HT_{1A}-enhancement model discussed above.
3. It is not clear from pharmacological challenge studies whether any effect is sufficient for antidepressant action because of the lack of correlation between effect and treatment response.
4. Even when different antidepressants have the same overall effect of enhancing 5-HT_{1A} receptor function, they appear to do it by different mechanisms. There is evidence that SSRIs and TCAs which inhibit reuptake of 5-HT achieve this via desensitization of presynaptic 5-HT_{1A} receptors but that TCAs which inhibit reuptake of noradrenaline, and lithium, achieve this in other ways. This may explain the different effects of acute TRP depletion following SSRI or TCA treatment in depressed patients (see below).
5. SSRIs, but not TCAs or lithium, desensitize postsynaptic 5-HT_{1A} receptors.
6. Pharmacological challenge studies do not produce a coherent picture for the action of antidepressants on 5-HT_2-mediated pathways although there may be differences between TCAs specifically inhibiting noradrenaline reuptake, resulting in decreased function, and those inhibiting 5-HT reuptake where increased responses have been reported.

Table 8.2. Effects of antidepressants on 5-HT function: Evidence from human drug challenge studies

Putative mechanism	TCA		SSRI	Receptor antagonists[a]	MAOIs	Lithium
	NA	NA+5-HT				
Presynaptic challenge (5-HT_{1A} mediated)	↑	↑	↑	→	↑	↑
Presynaptic 5-HT_{1A} receptor challenge	→	↓	↓	ND	ND	→
postsynaptic 5-HT_{1A} receptor challenge	→	→	↓	ND	ND	→
5-HT_{1D} receptor challenge	ND	ND	→	ND	ND	ND
Presynaptic challenge (5-HT_2 mediated)	↓/→	↑/→	↑/→	ND	↑	↑/→
Postsynaptic 5-HT_2 receptor challenge	(→)		↑/↓	ND	ND	ND

↑, increased responses; (), uncertain data; ↓, decreased responses; /, conflicting results; →, no effect; ND, no data; [a], trazodone and mianserin

7. The net effect of SSRIs on 5-HT_{1A} (and possibly 5-HT_2) neurotransmission may be due to the combination of increased presynaptic 'drive' together with some desensitization of postsysnaptic 5-HT_{1A} (and more speculatively 5-HT_2) receptors (i.e., analogous to pressing both the accelerator and brake). Reduction of the presynaptic drive by acute tryptophan depletion[122] (taking the foot off the accelerator) could then result in a large reduction in 5-HT function (unopposed effect of the brake) resulting in a sudden reversal of antidepressant effect. Given the apparent depressive relapse when tryptophan depletion or *p*-chlorophenylalanine are used in patients treated with MAOIs,[123,124] it is possible that postsynaptic 5-HT_{1A} receptors are also desensitized after such treatment but no pharmacological challenge studies have been reported which test this. In contrast if postsynaptic receptor sensitivity is unaltered, as with selective noradrenaline reuptake inhibitors or lithium, then reducing presynaptic drive could still allow sufficient neurotransmission to maintain the therapeutic effect in the short-term (analogous to the car 'coasting' without the brake applied). This could, at least in part, account for the lack of reversal of antidepressant effect after tryptophan depletion is used in patients treated with these drugs.[123,125]

References

1. Tatsumi M, Groshan K, Blakely RD et al. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. Eur J Pharmacol 1997; 340:249-258.
2. Charney DS, Menkes DB, Heninger GR. Receptor sensitivity and the mechanism of action of antidepressant treatment. Implications for the etiology and therapy of depression. Arch Gen Psychiatr 1981; 38:1160-1179.
3. Bourin M, Baker GB. Do G proteins have a role in antidepressant actions? Eur Neuropsychopharmacology 1996; 6:49-53.
4. Blier P, de Montigny C. Modification of 5-HT neuron properties by sustained administration of the 5-HT1A agonist gepirone: Electrophysiological studies in the rat brain. Synapse 1987; 1:470-480.
5. Blier P, de Montigny C. Current advances in the treatment of depression. Trends Pharmacol Sci 1994; 15:220-226.
6. Deakin JFW, Graeff FG. Critique: 5-HT and mechanisms of defence. J Psychopharmacol 1991; 5:305-315.
7. Bel N, Artigas F. Chronic treatment with fluvoxamine increases extracellular serotonin in frontal cortex but not in raphe nuclei. Synapse 1994; 15:243-245.
8. Goodwin GM, De Souza RJ, Green AR. Attenuation by electroconvulsive shock and antidepressant drugs of the 5-HT1A receptor-mediated hypothermia and serotonin syndrome produced by 8-OH-DPAT in the rat. Psychopharmacology 1987; 91:500-505.
9. Maj J, Moryl E. Effect of sertraline and citalopram given repeatedly on the responsiveness of 5-HT receptor subpopulations. J Neural Transm 1992; 88:143-156.
10. Li Q, Brownfield LS, Levy AD et al. Attenuation of hormone responses to the 5-HT1A agonist ipsapirone by long-term treatment with fluoxetine, but not desipramine, in male rats. Biol Psychiatry 1994; 36:300-308.
11. O'Donnell JM, Grealy M. Neuroendocrine response to clonidine and 8-OH-DPAT in rats following chronic administration of desipramine or sertraline. Eur J Pharmacol 1992; 105:863-868.
12. Aulakh CS, Wozniak KM, Hill JL et al. Differential effects of long-term antidepressant treatments on 8-OHDPAT-induced increases in plasma prolactin and corticosterone in rats. Eur J Pharmacol 1988; 156:395-400.
13. Hjorth S, Auerbach SB. Lack of 5-HT1A autoreceptor desensitization following chronic citalopram treatment, as determined by in vivo microdialysis. Neuropharmacology 1994; 33:331-334.
14. Cowen PJ. Pharmacological challenge tests and brain serotonin function in depression and during SSRI treatment. In: Briley M, Montgomery S, eds. Antidepressant therapy at the Dawn of the Third Millenium. London: Martin Dunitz, 1998:175-189.
15. Anderson IM, Cowen PJ. Clomipramine enhances prolactin and growth hormone responses to L-tryptophan. Psychopharmacology 1986; 89:131-133.
16. McCance SL, Cowen PJ, Waller H et al. The effect of metergoline on endocrine responses to L-tryptophan. J Psychopharmacol 1987; 1:90-94.
17. Smith CE, Ware CJ, Cowen PJ. Pindolol decreases prolactin and growth hormone responses to intravenous L-tryptophan. Psychopharmacology 1991; 103:140-142.
18. Charig EM, Anderson IM, Robinson JM et al. L-tryptophan and prolactin release: Evidence for interaction between 5-HT1 and 5-HT2 receptors. Hum Psychopharmacol 1986; 1:93-97.
19. Cowen PJ, Anderson IM. 5HT neuroendocrinology: Changes during depressive illness and antidepressant drug treatment. In: Deakin JFW, ed. The Biology of Depression. London: Gaskell, 1986:71-89.
20. Anderson I, Cowen PJ, Grahame-Smith DG. The effect of BRL 43694 on the neuroendocrine responses to L-tryptophan infusion. J Psychopharmacol 1988; 2(2):Abstract.
21. Gartside SE, Cowen PJ. Mediation of ACTH and prolactin responses to 5-HTP by 5-HT2 receptors. Eur J Pharmacol 1990; 179:103-109.
22. Nakai Y, Imura H, Sakurai H et al. Effect of cyproheptadine on human growth hormone secretion. J Clin Endocrinol Metab 1974; 38:446-449.

23. Lee MA, Nash JF, Barnes M et al. Inhibitory effect of ritanserin on the 5-hydroxytryptophan-mediated cortisol, ACTH and prolactin secretion in humans. Psychopharmacology 1991; 103:258-264.
24. Facchinetti F, Martignoni E, Nappi G et al. Ritanserin, a serotonin receptor antagonist does not prevent 5-hydroxytryptophan induced B-EP, B-LPH and cortisol secretion. Horm Res 1987; 27:42-46.
25. Meltzer HY, Maes M. Effect of pindolol on the L-5-HTP-induced increase in plasma prolactin and cortisol concentrations in man. Psychopharmacology 1994; 114:635-643.
26. CSM/MCA. Fenfluramine and dexfenfluramine withdrawn: Further cases of valvular heart disease. Curr Prob Pharmacovigil 1997; 23:13-14.
27. Coccaro EF, Kavoussi RJ, Cooper TB et al. Hormonal responses to d- and d,l-fenfluramine in healthy subjects. Neuropsychopharmacol 1996; 15:595-607.
28. Campbell DB. Dexfenfluramine: An overview of its mechanisms of action. Rev Contemp Pharmacol 1991; 2:93-113.
29. Shapira B, Reiss A, Kaiser N et al. Effect of imipramine treatment on the prolactin response to fenfluramine and placebo challenge in depressed patients. J Aff Disord 1989; 16:1-4.
30. Shapira B, Yagmur MJ, Gropp C et al. Effect of clomipramine and lithium on fenfluramine-induced hormone release in major depression. Biol Psychiatry 1992; 32:975-983.
31. O'Keane V, McLoughlin D, Dinan TG. D-fenfluramine-induced prolactin and cortisol release in major depression: Response to treatment. J Aff Disord 1992; 26:143-150
32. Monteleone P, Catapano F, Bortolotti F et al. Plasma prolactin response to d-fenfluramine in obsessive-compulsive patients before and after fluvoxamine treatment. Biol Psychiatry 1997; 42:175-180.
33. Goodall EM, Cowen PJ, Franklin M et al. Ritanserin attenuates anorectic, endocrine and thermic responses to d-fenfluramine in human volunteers. Psychopharmacology 1993; 112:461-466.
34. Coccaro EF, Kavoussi RJ, Oakes M et al. 5-HT2a/2c receptor blockade by amesergide fully attenuates prolactin response to d-fenfluramine challenge in physically healthy human subjects. Psychopharmacology 1996; 126:24-30.
35. Park SB, Cowen PJ. Effect of pindolol on the prolactin response to d-fenfluramine. Psychopharmacology 1995; 118:471-474.
36. Coccaro EF, Kavoussi RJ, Cooper TB et al. 5-HT3 receptor antagonism by ondansetron does not attenuate prolactin response to d-fenfluramine challenge in healthy human subjects. Psychopharmacology 1996; 127:108-112.
37. Curtis VA, Wright P, Reveley A et al. Effect of clozapine on d-fenfluramine-evoked neuroendocrine responses in schizophrenia and its relationship to clinical improvement. Br J Psychiatr 1995; 166:642-646.
38. Anderson IM, Ware CJ, da Roza Davis JM et al. Decreased 5-HT-mediated prolactin release in major depression. Br J Psychiatr 1992; 160:372-378
39. Anderson IM. 5-Hydroxytryptamine and depression: Studies using a neuroendocrine strategy. London University: M.D. Thesis, 1992.
40. Cowen PJ, Anderson IM, Grahame-Smith DG. Neuroendocrine effects of azapirones. J Clin Psychopharmacology 1990; 10:21S-25S.
41. Aghajanian GK, Spouse JS, Rasmussen K. Physiology of the midbrain serotonin system. In: Meltzer HY (ed) Psychopharmacology: The Third Generation of Progress. New York; Raven Press, 1987:141-149.
42. Shenker A, Maayani S, Weinstein H et al. Two 5-HT receptors linked to adenylate cyclase in guinea-pig hippocampus are discriminated by 5-carboxamidotryptamine and spiperone. Eur J Pharmacol 1985; 109:427-429.
43. Markstein R, Hoyer D, Engel D. 5-HT1A receptors mediate stimulation of adenylate cyclase in rat hippocampus. Naunyn-Schmeideberg's Arch Pharmacol 1986; 333:335-341.
44. Andrade R. Electrophysiology of 5-HT1A receptors in the rat hippocampus and cortex. Drug Develop Res 1992; 26:275-286.
45. Anderson IM, Cowen PJ. Effect of pindolol on endocrine and temperature responses to buspirone in healthy volunteers. Psychopharmacology 1992; 106:428-432.

46. Lesch CP, Sohnle K, Poten B et al. Corticotropin and cortisol secretion after central 5-hydroxytryptamine-1A (5-HT1A) receptor activation: Effects of 5-HT receptor and β-adrenoceptor antagonists. J Clin Endocrinol Metab 1990; 70:670-674.
47. Lesch KP, Poten B, Schulte HM. Pharmacology of the hypothermic response to 5-HT1A receptor activation in humans. Eur J Clin Pharmacol 1990; 39:17-19.
48. Anderson IM. Serotonin, gastric emptying, and dyspepsia. Br Med J 1992; 305:1295.
49. Goodwin GM, De Souza RJ, Green AR. The pharmacology of the hypothermic response in mice to 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT): A model of presynaptic 5-HT1 function. Neuropharmacology 1985; 24:1187-1194.
50. Martin KF, Phillips I, Hearson M et al. Characterization of 8-OH-DPAT-induced hypothermia in mice as a 5-HT1A autoreceptor response and its evaluation as a model to selectively identify antidepressants. Br J Pharmacol 1992; 107:15-21.
51. Goodwin GM, De Souza RJ, Green AR et al. The pharmacology of the behavioural and hypothermic responses of rats to 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT). Psychopharmacology 1987; 91:506-511.
52. Hjorth S. Hypothermia in the rat induced by the potent serotoninergic agent 8-OH-DPAT. J Neural Transm 1985; 61:131-135
53. Hillegaart V. Effects of local application of 5-HT and 8-OH-DPAT into the dorsal and median raphe nuclei on core temperature in the rat. Psychopharmacology 1991; 103:291-296.
54. O'Connell MT, Sarna GS, Curzon G. Evidence for postsynaptic mediation of the hypothermic effect of 5-HT1A receptor activation. Br J Pharmacol 1992; 106:603-609.
55. Blier P, Seletti B, Young SN et al. Serotonin1A receptor activation and hypothermia: Evidence for a postsynaptic mechanism in humans. Neuropsychopharmacol 1994; 10:S92.
56. Franceschini R, Cataldi A, Garibaldi A et al. The effects of sumatriptan on pituitary secretion in man. Neuropharmacology 1994; 33:235-239.
57. Herdman JR, Delva NJ, Hockney RE et al. Neuroendocrine effects of sumatriptan. Psychopharmacology 1994; 113:561-564.
58. Boeles S, Williams C, Campling GM et al. Sumatriptan decreases food intake and increases plasma growth hormone in healthy women. Psychopharmacology 1997; 129:179-182.
59. Sciberras DG, Polvino WJ, Gertz WJ et al. Initial human experience with MK-462 (rizatriptan): a novel 5-HT1D agonist. Br J Clin Pharmacol 1997; 43:49-54.
60. Chopin P, Moret C, Briley M. Neuropharmacology of 5-hydroxytryptamine1B/D receptor ligands. Pharmacol Ther 1994; 62:385-405.
61. Charney DS, Woods SW, Goodman WK et al. Serotonin function in anxiety. II. Effects of the serotonin agonist MCPP in panic disorder patients and healthy subjects. Psychopharmacology 1987; 92:14-24
62. Murphy DL, Mueller EA, Hill JL et al. Comparative anxiogenic, neuroendocrine, and other physiologic effects of m-chlorophenylpiperazine given intravenously or orally to healthy volunteers. Psychopharmacology 1989; 98:275-282
63. Hoyer D. Functional correlates of the serotonin 5-HT1 recognition sites. J Recept Res 1988; 8:59-81.
64. Hamik A, Peroutka SJ. l-(m-chlorophenyl)piperazine (mCPP) interactions with neurotransmitter receptors in the human brain. Biol Psychiatry 1989; 25:569-575.
65. Murphy DL, Lesch KP, Aulakh CS et al. Serotonin-selective arylpiperazines with neuroendocrine, behavioral, temperature and cardiovascular effects in humans. Pharmacol Rev 1991; 43:527-552.
66. Baumann MH, Rutter JJ, Auerbach SB. Intravenous administration of the serotonin agonist m-chlorophenylpiperazine (mCPP) increases extracellular serotonin in the diencephalon of awake rats. Neuropharmacology 1993; 32:1381-1386.
67. Baumann MH, Mash DC, Staley JK. The serotonin agonist m-chlorophenylpiperazine (mCPP) binds to serotonin transporter sites in human brain. Neuroreport 1995; 6:2150-2152.
68. Kahn RS, Kalus O, Wetzler S et al. Effects of serotonin antagonists on m-chlorophenylpiperazine-mediated responses in normal subjects. Psychiatry Res 1990; 33:189-198.

69. Pigott TA, Hill JL, Grady TA et al. A comparison of the behavioural effects of oral versus intravenous mCPP administration in OCD patients and the effect of metergoline prior to IV mCPP. Biol Psychiatry 1993; 33:3-14.
70. Seibyl JP, Krystal JH, Price LH et al. Effects of ritanserin on the behavioral, neuroendocrine and cardiovascular responses to meta-chlorophenylpiperazine in healthy human subjects. Psychiatry Res 1991; 38:227-236.
71. Breier A, Kirkpatrick B, Buchanan RW. Clozapine attenuates meta-chlorophenylpiperazine (mCCP)-induced plasma cortisol increase in schizophrenia. Biol Psychiatry 1993; 34:492-494.
72. Kahn RS, Davidson M, Siever LJ et al. Clozapine treatment and its effect on neuroendocrine responses induced by the serotonin agonist, m-chlorophenylpiperazine. Biol Psychiatry 1994; 35:909-912.
73. Silverstone PH, Cowen PJ. The 5-HT3 antagonist, BRL 46470 does not attenuate m-chlorophenylpiperazine (mCPP)-induced changes in human volunteers. Biol Psychiatry 1994; 36:309-316.
74. Broocks A, Briggs NC, Pigott TA et al. Behavioral, physiological and neuroendocrine responses in healthy volunteers to m-chlorophenylpiperazine (m-CPP) with and without ondansetron pretreatment. Psychopharmacology 1997; 130:91-103.
75. Koenig IJ, Gudelsky GA, Meltzer HY. Stimulation of corticosterone and β-endorphin secretion in the rat by selective 5-HT receptor subtype activation. Eur J Pharmacol 1987; 137:1-8.
76. Van de Kar LD, Lorens SA, Urban JH et al. Effect of selective serotonin (5-HT) agonists and 5-HT2 antagonists on prolactin secretion. Neuropharmacology 1989; 28:299-305.
77. King BH, Brazell C, Dourish CT et al. MK-212 increases rat plasma ACTH concentration by activation of 5-HT1C receptor subtype. Neurosci Lett 1989; 105:174-176.
78. Lowy MT, Meltzer HY. Stimulation of serum cortisol and prolactin secretion in humans by MK-212, a centrally active serotonin agonist. Biol Psychiatry 1988; 23:818-828.
79. Meltzer HY, Maes M. Effect of pindolol pretreatment on MK-212-induced plasma cortisol and prolactin responses in normal men. Biol Psychiatry 1995; 38:310-318.
80. Fineberg NA, Cowen PJ, Kirk JW et al. Neuroendocrine responses to intravenous L-tryptophan in obsessive compulsive disorder. J Aff Disord 1994; 32:97-104.
81. Fineberg NA, Roberts A, Montgomery SA et al. Brain 5-HT function in obsessive-compulsive disorder: Prolactin responses to d-fenfluramine. Br J Psychiatr 1997; 171:280-282.
82. Sargent PA, Williamson DJ, Cowen PJ. Brain 5-HT neurotransmission during paroxetine treatment. Br J Psychiatr 1998; 172:49-52.
83. Richelson E. Synaptic effects of antidepressants. J Clin Psychopharmacol 1996; 16:1S-9S.
84. Cowen PJ, Geaney DP, Schachter M et al. Desipramine treatment in normal subjects. Effects on neuroendocrine responses to tryptophan and on platelet serotonin (5-HT)-related receptors. Arch Gen Psychiatr 1986; 43:61-67.
85. Charney DS, Heninger GR, Sternberg DE. Serotonin function and mechanism of action of antidepressant treatment. Arch Gen Psychiatr 1984; 41:359-365.
86. Price LH, Charney DS, Delgado PL et al. Effects of desipramine and fluvoxamine treatment on the prolactin response to tryptophan. Arch Gen Psychiatr 1989; 46:625-631.
87. Cowen PJ, McCance SL, Gelder MG et al. Effect of amitriptyline on endocrine responses to intravenous L-tryptophan. Psychiatry Res 1990; 31:201-208.
88. Anderson IM, Parry-Billings M, Newsholme EA et al. Dieting reduces plasma tryptophan and alters brain 5-HT function in women. Psychol Med 1990; 20:785-791.
89. Herdman JRE, Cowen PJ, Campling GM et al. Effect of lofepramine on 5-HT function and sleep. J Aff Disord 1993; 29:63-72.
90. Lesch K-P, Disselkamp-Tietze J, Schmidtke A. 5-HT1A receptor function in depression: effect of chronic amitriptyline treatment. J Neural Transm 1990; 80:157-161.
91. da Roza Davis JM, Ware CJ, Anderson IM et al. Desensitization of 5-HT1A autoreceptors by tricyclic antidepressant treatment. J Psychopharmacol 1992; 6:118.
92. Baraban JM, Aghajanian GK. Suppression of firing activity of 5-HT neurons in the dorsal raphe by alpha-adrenoceptor antagonists. Neuropharmacology 1980; 19:355-363.

93. Baraban JM, Aghajanian GK. Noradrenergic innervation of serotonergic neurons in the dorsal raphe: Demonstration by electron microscopic autoradiography. Brain Res 1981; 204:1-11.
94. Frankhuyzen AL, Mulder AH. Pharmacological characterisation of presynaptic α-adrenoceptors modulating ^{3}H-5-hydroxytryptamine release from rat hippocampus. Eur J Pharmacol 1982; 81:97-106.
95. Gothert M, Huth H, Schlicker E. Characterization of the receptor subtype involved in α-adrenoceptor-mediated modulation of serotonin release from rat brain cortex slices. Naunyn-Schmiedeberg's Arch Pharmacol 1981; 317:199-203.
96. Schittecatte M, Charles G, Nefve C et al. Long-term downregulation of central adrenoceptor function by desipramine treatment: A clonidine study in normal subjects. Biol Psychiatry 1992; 31:856-858.
97. Meltzer HY. Role of serotonin in depression. Ann NY Acad Sci 1990; 600:486-500.
98. Kasper S, Vieira A, Schmidt R et al. Multiple hormone responses to stimulation with dl-fenfluramine in patients with major depression before and after antidepressive treatment. Pharmacopsychiatry 1990; 23:76-84.
99. Stahl SM, Hauger RL, Rausch JL et al. Downregulation of serotonin receptor subtypes by nortriptyline and adinazolam in major depressive disorder: Neuroendocrine and platelet markers. Clin Neuropharmacol 1993; 16:S19-S32.
100. Leatherman ME, Ekstrom RD, Corrigan M et al. Central serotonergic changes following antidepressant treatment: A neuroendocrine assessment. Psychopharmacol Bull 1993; 29:149-154.
101. Lesch KP, Hoh A, Schulte HM et al. Long-term fluoxetine treatment decreases 5-HT1A receptor responsivity in obsessive-compulsive disorder. Psychopharmacology 1991; 105:415-420.
102. Anderson IM, Deakin JFW, Miller HEJ. The effect of chronic fluvoxamine on hormonal and psychological responses to buspirone in normal volunteers. Psychopharmacology 1996; 128:74-82.
103. Wing YK, Clifford EM, Sheehan BD et al. Paroxetine treatment and the prolactin response to sumatriptan. Psychopharmacology 1996; 124:377-399.
104. Hollander E, DeCaria C, Gully R et al. Effects of chronic fluoxetine treatment on behavioral and neuroendocrine responses to meta-chlorophenylpiperazine in obsessive-compulsive disorder. Psychiatry Res 1991; 37:1-7.
105. Quested DJ, Sargent PA, Cowen PJ. SSRI treatment decreases prolactin and hyperthermic responses to mCPP. Psychopharmacology 1997; 133:305-308.
106. Price LH, Charney DS, Heninger GR. Effects of tranylcypromine treatment on neuroendocrine, behavioral and autonomic responses to tryptophan in depressed patients. Life Sci 1985; 37:809-818.
107. Meltzer HY, Lowry MT, Robertson A et al. Effects of 5-hydroxytryptophan on serum cortisol levels in major affective disorders. III. Effect of antidepressants and lithium. Arch Gen Psychiatr 1984; 41:391-402.
108. Cowen PJ. Prolactin response to tryptophan during mianserin treatment. Am J Psychiatr 1988; 145:740-741.
109. Price LH, Charney DS, Heninger GR. Effects of trazodone treatment on serotonergic function in depressed patients. Psychiatry Res 1988; 24:165-175.
110. Walsh AES, Hockney RA, Campling G et al. Neuroendocrine and temperature effects of nefazodone in healthy volunteers. Biol Psychiatry 1993; 33:115-119.
111. Walsh AE, Cowen PJ. Attenuation of the prolactin-stimulating and hyperthermic effects of nefazodone after subacute treatment. J Clin Psychopharmacol 1994; 14:268-273.
112. Benjamin J, Greenberg BD, Murphy DL. Daily administration of m-chlorophenylpiperazine to healthy human volunteers rapidly attenuates many of its behavioral, hormonal, cardiovascular and temperature effects. Psychopharmacology 1996; 127:140-149.
113. McCance SL, Cohen PR, Cowen PJ. Lithium increases 5-HT-mediated PRL release. Psychopharmacology 1989; 99:276-281.

114. Glue PW, Cowen PJ, Nutt DJ et al. The effect of lithium on 5-HT-mediated neuroendocrine responses and platelet 5-HT receptors. Psychopharmacology 1986; 90:398-402.
115. Price LH, Charney DS, Delgado PL et al. Lithium and serotonergic function: Neuroendocrine and behavioural responses to intravenous tryptophan in affective disorder. Arch Gen Psychiatr 1989; 46:13-19.
116. Cowen PJ, McCance SL, Ware CJ et al. Lithium in tricyclic-resistant depression: Correlation of increased brain 5-HT function with clinical outcome. Br J Psychiatr 1991; 159:341-346.
117. Manji HK, Hsiao JK, Risby ED et al. The mechanisms of action of lithium. I. Effects in serotonergic and noradrenergic systems in normal subjects. Arch Gen Psychiatr 1991; 48:505-511.
118. Walsh AE, Ware CJ, Cowen PJ. Lithium and 5-HT1A receptor sensitivity: A neuroendocrine study in healthy volunteers. Psychopharmacology 1991; 105:568-572.
119. Baraban JM, Worley PF, Snyder SH. Second messenger systems and psychoactive drug action: focus on the phosphoinositide system and lithium. Am J Psychiatr 1989; 146:1251-1260.
120. Power AC, Dorkins CE, Cowen PJ. Effect of lithium on the prolactin response to D-fenfluramine in healthy subjects. Biol Psychiatry 1993; 33:801-805.
121. El Mansari M, Bouchard C, Blier P. Alteration of serotonin release in the guinea pig orbitofrontal cortex by selective serotonin reuptake inhibitors: Relevance to treatment of obsessive-compulsive disorder. Neuropsychopharmacol 1995; 13:117-127.
122. Young SN, Smith SE, Pihl R et al. Tryptophan depletion causes a rapid lowering of mood in normal males. Psychopharmacology 1985; 87:173-177.
123. Delgado PL, Charney DS, Price LH et al. Serotonin function and the mechanism of antidepressant action: Reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan. Arch Gen Psychiatr 1990; 47:411-418.
124. Shopsin B, Friedman E, Gershon S. Parachlorophenylalanine reversal of tranylcypromine effects in depressed patients. Arch Gen Psychiatr 1976; 33:811-819.
125. Benkelfat C, Seletti B, Palmour RM et al. Tryptophan depletion in stable lithium-treated patients with bipolar disorder in remission. Arch Gen Psychiatr 1995; 52:154-155.

CHAPTER 9

SSRI-Induced Functional Changes in Serotonergic Neurons

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The term 'SSRIs' encompasses several chemical agents that have in common their ability to inhibit selectively the function of the serotonin (5-hydroxytryptamine, 5-HT) transporter. This is located on the membranes of serotonergic and glial cells of the brain and other cells outside the central nervous system (CNS), such as platelets, enterochromaffin cells of the gut, endothelial cells and mastocytes. The 5-HT transporter was cloned in 1991 from different cellular sources.[1,2] It belongs to the same family as dopamine or noradrenaline transporters and is characterized by the presence of 12 transmembrane domains and intracellular N- and C-terminals.[3] The cloned transporter displays the same pharmacological profile as the native protein expressed in brain preparations[4-6] (e.g., synaptosomes or brain slices) and was soon recognized as sharing the identity of the CNS and peripheral 5-HT transporter in humans.[7,8]

By virtue of their ability to interfere with the process of internalization of 5-HT molecules via the 5-HT transporter, the SSRIs enhance the ratio of the concentrations of the extra- and intracellular compartments of 5-HT. Work using in vitro techniques to measure 5-HT uptake in brain preparations (e.g., brain slices or synaptosomes) and ex vivo neurochemical models led to the conclusion that SSRIs enhance serotonergic transmission by increasing the concentration of the transmitter in the interstitial brain space. However, work carried out in vivo, using single-unit recording in the dorsal raphé nucleus (DRN) and in vivo microdialysis, has provided a more complex view of the actions of SSRIs in brain.[9] This chapter will summarize this evidence and will also focus on new therapeutic strategies based on these observations.

Inhibition of 5-HT Reuptake, Serotonergic Cell Firing and 5-HT Release

The systemic administration of single doses of selective and non-selective 5-HT reuptake inhibitors decreases the firing frequency of serotonergic neurons of the DRN.[10-13] Similarly, the administration of tricyclic drugs that inhibit the reuptake of noradrenaline reduces the firing of noradrenergic neurons of the locus coeruleus.[10,11] Microdialysis studies have shown that this effect in the DRN is due to an increase in the extracellular concentration of 5-HT in the vicinity of cell bodies of serotonergic neurons of the dorsal and median (MRN) raphé nuclei.[14-19] In this manner, 5-HT reuptake inhibitors behave as indirect agonists of somatodendritic 5-HT_{1A} autoreceptors (see below). This effect was first demonstrated for the non-selective 5-HT reuptake inhibitor, clomipramine,[14] and later for the SSRIs.[15-19] In all cases examined, the application of 5-HT reuptake inhibitors, either systemically or by

Selective Serotonin Reuptake Inhibitors (SSRIs): Past, Present and Future, edited by S. Clare Stanford. ©1999 R.G. Landes Company.

reverse dialysis (i.e., dissolved in the fluid used to perfuse the microdialysis probes), increased markedly the extracellular concentration of 5-HT in the raphé nuclei of the midbrain.[14-19] The elevation of the 5-HT concentration in the extracellular raphé space is due to the presence of: 1) a high density of 5-HT reuptake sites in the raphé nuclei[20,21] (particularly in the DRN) and 2) release of 5-HT within the raphé nuclei which is greater than in forebrain.[14,22-25] Although the precise origin of the extracellular 5-HT found in the DRN and MRN is not known, it is likely that it is released by dendrites and by the proximal segments of efferent axons within the boundaries of the nuclei. Indeed, immunostaining of the DRN and MRN reveals the presence of a high density of serotonergic fibers in these locations.[26] The administration of SSRIs interferes with the reuptake process by serotonergic elements and increases the concentration of 5-HT in the extracellular compartment. Interestingly, the density of 5-HT reuptake sites in the midbrain raphé nuclei is higher than in any other area in the rat and human brain,[20,21] which supports the idea that these nuclei are particularly sensitive to the action of SSRIs. Figure 9.1 shows the maximal absolute increments of the extracellular 5-HT concentration produced in six different brain areas after the systemic administration of three different doses of fluoxetine (1, 3 and 10 mg/kg i.p.). In common with other SSRIs, the 5-HT increments produced by fluoxetine in the midbrain are larger than in any other forebrain area examined so far. Interestingly, despite the low number of serotonergic neurons in the MRN, this nucleus appears to be highly sensitive to the action of fluoxetine.[27a]

The presence of 5-HT_{1A} autoreceptors on serotonergic neurons is a key element in the regional selectivity of SSRIs. 5-HT_{1A} receptors are located in the somatodendritic region of serotonergic neurons (presynaptic) and on other neuronal types (postsynaptic, mostly on pyramidal neurons in the cortex and hippocampus).[28-30] 5-HT_{1A} receptors are coupled to a K^+ channel via a pertussis toxin-sensitive G protein.[31,32] In the hippocampus, inhibition and activation of adenylyl cyclase have also been reported as effector systems but these are apparently lacking in the DRN.[33-35] The activation of raphé 5-HT_{1A} receptors by selective 5-HT_{1A} receptor agonists leads to a reduction in 5-HT synthesis and release in the forebrain.[36,37] Likewise, the excess extracellular 5-HT produced by SSRIs in the DRN and MRN activates somatodendritic 5-HT_{1A} autoreceptors and reduces 5-HT release in the projection areas of these two nuclei, such as frontal cortex, striatum and, to a lesser extent, the hippocampus[19,38] (see below). Thus, the local administration of clomipramine or citalopram in the vicinity of the DRN and MRN elicits a dramatic elevation of the extracellular 5-HT concentration in these nuclei which is accompanied by an approximately 50% reduction in 5-HT release in frontal cortex.[14,19] This effect is counteracted by the selective 5-HT_{1A} receptor antagonist, *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride) WAY 100635, which supports the exclusive participation of this receptor subtype in the attenuation of terminal 5-HT release induced by this procedure.[19]

Non-selective 5-HT_{1A} receptor antagonists, such as (-)pindolol or (-)tertatolol, are also capable of preventing the reduction in 5-HT release induced in a DRN-innervated area following the application of citalopram in midbrain.[39,40] These microdialysis results are paralleled by single-unit recording studies showing that 5-HT_{1A} receptor antagonists can prevent or reverse the inhibition of serotonergic cell firing induced by SSRIs.[17,41,42]

Regional Selectivity of the Inhibitory Action of SSRIs on 5-HT Release

SSRIs inhibit the 5-HT release in forebrain in a heterogeneous and regionally-dependent manner. Release is more markedly inhibited in areas innervated preferentially by DRN serotonergic fibers, like frontal cortex or dorsal striatum, compared with the dorsal or the

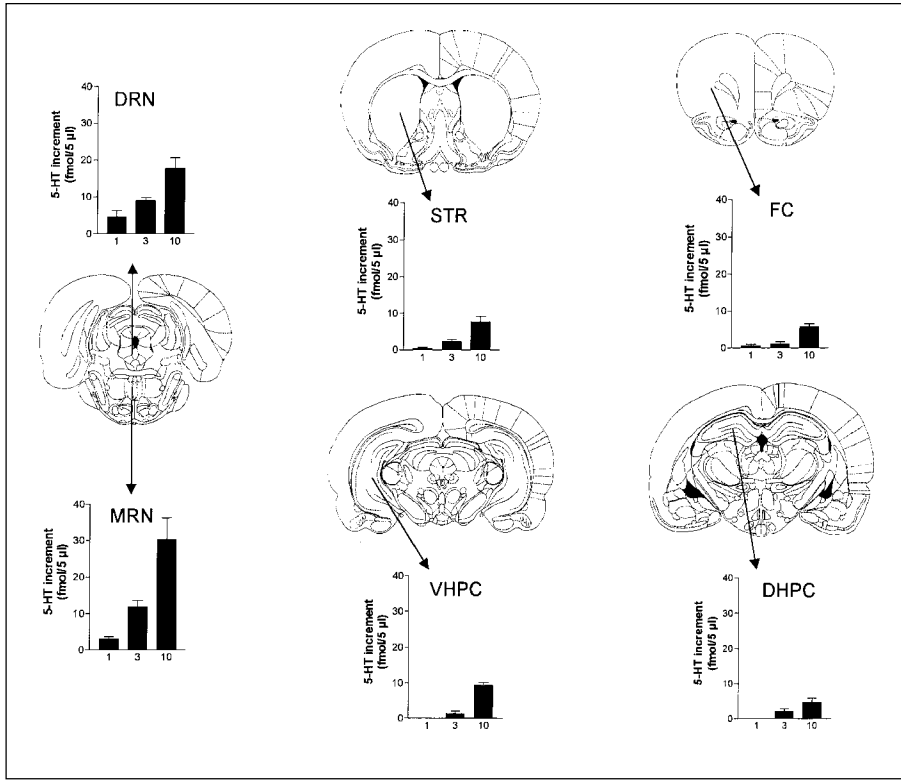

Fig. 9.1. Maximal increments of the 5-HT output (fmol 5-HT per 20 min dialysate fraction, expressed for a probe tip of 1.5 mm), induced by 1, 3 and 10 mg/kg of the SSRI, fluoxetine, in the dorsal raphé nucleus (DRN) and median raphé nucleus (MRN) of the midbrain and forebrain regions with selective or preferential innervation from the DRN [dorsal striatum (STR) and frontal cortex (FC)] and the MRN [dorsal and ventral hippocampus (DHPC and VHPC, respectively)].[27a] Note that the increase in 5-HT concentrations in the DRN and MRN are larger than in projection areas of both nuclei. Coronal sections of the rat brain are reprinted with permission from: Paxinos G, Watson C (CD-ROM edition).[27b] ©1997 Academic Press.

ventral hippocampus[19,38] which receive a prominent serotonergic innervation from the MRN, particularly the former region.[43,44] Figure 9.2 shows the effects of local administration of fluoxetine in the DRN or MRN on 5-HT release in frontal cortex and dorsal hippocampus, respectively, in rats implanted with two dialysis probes. The local application of 300 µM fluoxetine in the DRN led to an elevation of 5-HT to 727 ± 86% of baseline which later stabilized at approximately 450% ($P<0.001$) (Fig. 9.2A). This was accompanied by a significant reduction of the cortical dialysate 5-HT concentration to 56 ± 11% of baseline values (peak reduction) (Fig. 9.2B). The subcutaneous administration of WAY-100635 (1 mg/kg) caused the dialysate 5-HT concentration to return to baseline in the frontal cortex and further elevated 5-HT to 850% of baseline in the DRN ($P < 0.001$). The application of fluoxetine (300 µM) in the MRN caused a five-fold elevation of dialysate 5-HT concentration in this area (Fig. 9.2C). A moderate and steady decline was observed in the dorsal hippocampus

(Fig. 9.2D); this was not different from that observed in rats not administered the SSRI. The spontaneous reduction of 5-HT release in hippocampus (but not the striatum or frontal cortex) was also observed in one-day microdialysis experiments in freely-moving rats when the dialysis probes were perfused with artificial CSF containing 1 μM of the reuptake blocker citalopram. Its origin is unknown at present. [45,46]

A similar regional selectivity of the inhibitory action of SSRIs on forebrain 5-HT release has also been observed using citalopram (Fig. 9.3). The application of citalopram (50 μM) increased the 5-HT output in the DRN and MRN more than did fluoxetine. This is probably due to the higher affinity of citalopram for the 5-HT transporter. As observed with fluoxetine, the reduction in 5-HT release in frontal cortex during application of citalopram in the DRN was larger than that seen in the dorsal hippocampus during infusion of this drug into the MRN.

Evidence for the inhibitory action of SSRIs on 5-HT release also emerges from a different experimental procedure in which rats are implanted with one microdialysis probe in the forebrain which is perfused with a dialysis fluid supplemented with an SSRI (e.g., 1 μM citalopram) so as to inhibit 5-HT reuptake into brain tissue close to the dialysis probe. Under these conditions, the systemic administration of an SSRI causes little additional inhibition of 5-HT reuptake in this brain area. However, it does inhibit 5-HT reuptake in the raphé nuclei of the midbrain; this results in activation of 5-HT_{1A} autoreceptors and a reduction of 5-HT release in forebrain.[38,47] As shown in Figure 9.4 the intraperitoneal administration of paroxetine elicited an immediate and pronounced reduction of terminal release of 5-HT in the striatum which was reversed by the administration of the selective 5-HT_{1A} receptor antagonist, WAY 100635. In agreement with the data obtained in dual-probe experiments, a less marked effect was noted in the dorsal hippocampus after administration of the same dose of paroxetine. The involvement of raphé 5-HT_{1A} receptors in the reduction of 5-HT release is shown by the antagonism of this effect by the administration of WAY 100635 into the DRN (Fig. 9.4). The systemic administration of selective (UH-301, WAY-100135, WAY-100635) and non-selective (pindolol, penbutolol) 5-HT_{1A} receptor antagonists prevents the reduction of 5-HT release in the ventral hippocampus of anesthetized rats produced by the administration of SSRIs and non-selective 5-HT reuptake inhibitors.[48-50]

The reason(s) for the uneven reduction in 5-HT release in the forebrain induced by SSRIs, an effect which is also shared by 5-HT_{1A} receptor agonists, is unclear. It was first argued that DRN neurons might be more sensitive than MRN neurons to the inhibitory actions of 5-HT_{1A} receptor activation,[51] perhaps due to the presence of a larger receptor reserve. In accordance with this, the local administration of 8-OH-DPAT into the DRN and MRN preferentially inhibited 5-HT synthesis in DRN projection areas.[37] Yet, more recently it was found that 8-OH-DPAT and paroxetine inhibited the firing of DRN and MRN neurons with equal potency.[52] Moreover, recent microdialysis studies have revealed that the 5-HT release in the MRN is slightly more sensitive than that in the DRN due to the action of three different 5-HT_{1A} receptor agonists, 8-OH-DPAT, alnespirone and ipsapirone, despite evidence that these agents inhibited the 5-HT release more in the cortex or striatum than in the hippocampus.[45,46,53] It is thus likely that additional factors limit the effect of SSRIs in a region-dependent manner.

Among these, terminal autoreceptors also contribute to the dampening of the increase of extracellular 5-HT induced by SSRIs. These are of the 5-HT_{1B} receptor subtype and are negatively coupled to adenylyl cyclase.[54] Their activation reduces 5-HT release in vitro and in vivo.[55-58] Therefore, they play a significant role in the attenuation of the effects of SSRIs. This role is possibly less important than that of 5-HT_{1A} autoreceptors because the latter are exposed to higher 5-HT concentrations during SSRI treatments (i.e., SSRIs increase preferentially the 5-HT output in midbrain).

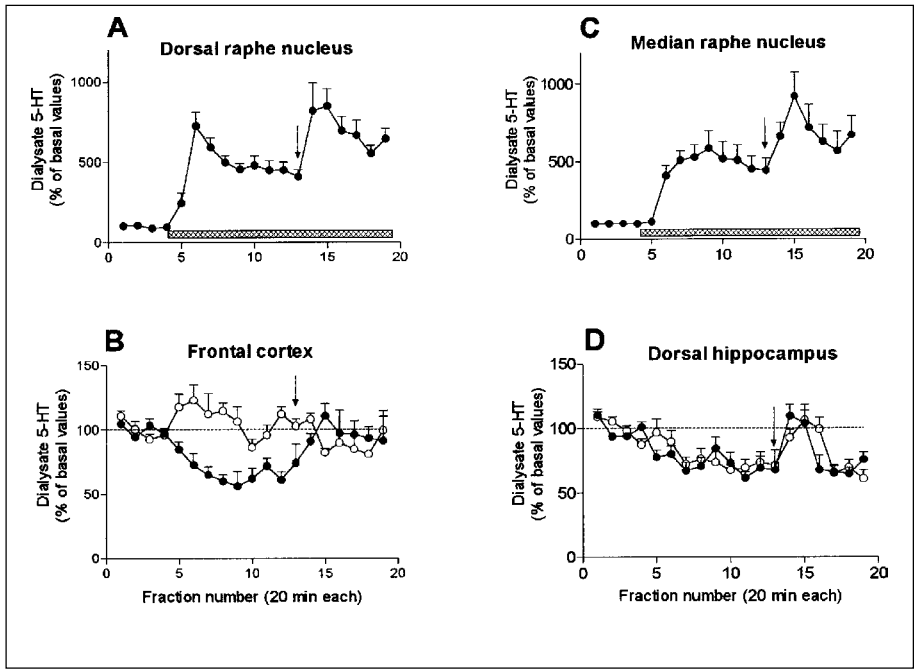

Fig. 9.2. Dual-probe microdialysis experiments. (A) Elevation of the dialysate 5-HT concentration in the DRN during application of 300 μM fluoxetine by reverse dialysis (shown by a cross-hatched bar) through a 1.5 mm dialysis probe (N=4; baseline 5-HT: 11.2±2.0 fmol/fraction). The arrow marks a s.c. injection of WAY-100635 (1 mg/kg). (B) Reduction of dialysate 5-HT in the frontal cortex during application of fluoxetine in the DRN (Probe tip: 1.5 mm; baseline 5-HT in presence of 1 μM citalopram: 8.4±0.6 fmol/fraction). The administration of WAY-100635 (arrow) returned 5-HT values to pre-fluoxetine levels. Dialysate 5-HT values in frontal cortex of saline-treated rats are shown by open circles. (C) Elevation of the dialysate 5-HT concentration in the MRN after the application of 300 μM fluoxetine by reverse dialysis (shown by a cross-hatched bar) through a 1.5 mm dialysis probe (N=7; baseline 5-HT: 10.3±1.6 fmol/fraction). The arrow marks a s.c. injection of WAY-100635 (1 mg/kg). (D) Reduction of dialysate 5-HT in dorsal hippocampus caused by the application of fluoxetine in the MRN (probe tip: 1.5 mm; baseline 5-HT in presence of 1 μM citalopram: 6.1±0.9 fmol/fraction). The decline produced by fluoxetine was comparable with that found in saline-treated rats (open circles).

Functional Changes in Serotonergic Neurons Induced by the Chronic Administration of SSRIs

Following long-term SSRI administration a progressive desensitization of 5-HT_{1A} autoreceptors occurs, as assessed by electrophysiological and other functional measures.[13,59] Apparently, this is not accompanied by changes in receptor density[38,60] which suggests that disruption of the functional uncoupling between the receptor and the G protein is a likely cause of this effect.

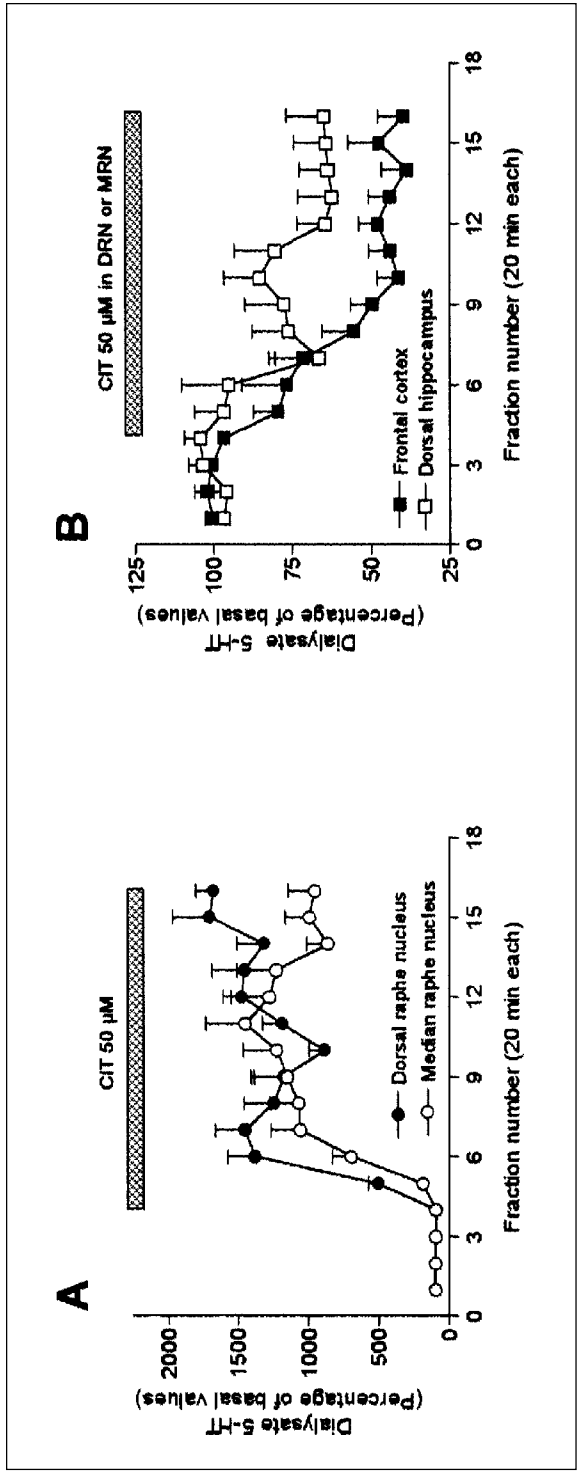

Fig. 9.3. Dual-probe microdialysis experiments. (A) The application of citalopram (50 mM) in the DRN (shown by a horizontal cross-hatched bar) elevated the 5-HT output locally and reduced it in the frontal cortex (B) to approximately 40% of baseline in rats implanted with two dialysis probes. In a parallel experiment, application of citalopram in the MRN (A) caused a significantly smaller reduction in the release of 5-HT in dorsal hippocampus (B). Data redrawn from ref. 19.

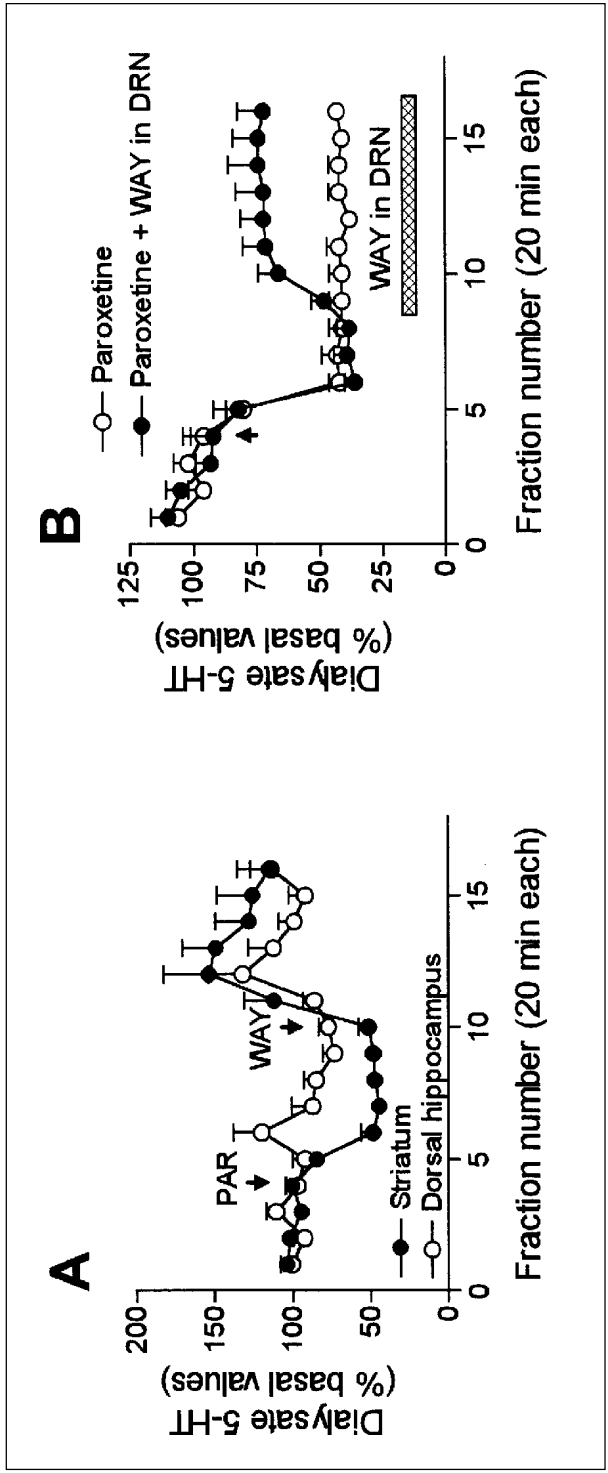

Fig. 9.4. (A) The administration of 3 mg/kg i.p. paroxetine (first arrow) reduced the 5-HT output significantly more in dorsal striatum (filled circles) than in the dorsal hippocampus (open circles) in conditions of local blockade of the 5-HT reuptake (1 μM citalopram in the perfusion fluid). The adminstration of 1 mg/kg of the selective 5-HT_{1A} antagonist WAY-100635 (second arrow) reversed the paroxetine-induced reduction. (B) The reduction of the 5-HT out put in frontal cortex induced by 3 mg/kg i.p. paroxetine under the same experimental conditions (open circles) was antagonized by the infusion of WAY 100635 (100 μM) in the DRN by reverse dialysis (cross hatched bar), thus demonstrating the involvement of raphé 5-HT_{1A} autoreceptors in the paroxetine-induced reduction of the cortical 5-HT output. Data redrawn from ref. 19.

The continuous (with mini-pumps) or repeated administration of SSRIs generally induces increases in extracellular 5-HT in the frontal cortex (but not the hippocampus) which are greater than those observed after single treatment with the same doses of test drugs.[61-65] This effect is likely to be attributable to the desensitization of 5-HT_{1A} receptors induced by the excess 5-HT in the DRN. The reduction in the effectiveness of the 5-HT_{1A} receptor-mediated negative feedback would enable serotonergic neurons to recover normal firing and terminal release. However, despite current views on this topic (summarized in Fig. 9.5., see below), the SSRI-induced desensitization of 5-HT_{1A} autoreceptors is probably incomplete since the administration of a 5-HT_{1A} receptor antagonist increases DRN serotonergic cell firing and terminal release in rats chronically treated with the SSRI citalopram.[42,66]

Potentiation of the Effects of SSRIs by 5-HT Autoreceptor Antagonists: Experimental Studies

Figure 9.5 shows schematically the changes in the function of serotonergic neurons induced by SSRIs. Under normal conditions, serotonergic neurons of the DRN discharge at a slow and regular firing rate (1-5 spikes/s). The single or short-term administration of SSRIs inhibits 5-HT reuptake in the forebrain and midbrain which should result in a generalized increase of the extracellular 5-HT concentration in brain. However, this increment is limited by two subsets of autoreceptors, 5-HT_{1A} and 5-HT_{1B} located on the somatodendritic and axonal portions of serotonergic neurons, respectively. 5-HT_{1A} receptors appear to play a predominant role in this effect as they are activated by 5-HT more than are terminal autoreceptors during SSRI treatments (compare the increments of the extracellular 5-HT concentration in midbrain and forebrain in Fig. 9.1). Following the repeated administration of SSRIs, a progressive desensitization of autoreceptors occurs due to the excess 5-HT in the extracellular brain compartment. This results in a reduction of the negative feedback exerted by the autoreceptors, which enables a normalization of cell firing and release of 5-HT by serotonergic neurons. In this situation, the administration of SSRIs enhances the 5-HT concentration in the terminal fields of serotonergic neurons more than does a single treatment.

From the above it can be hypothesized that the experimental and clinical effects of SSRIs would be potentiated by the concurrent administration of autoreceptor antagonists.[67] At the neurochemical level, this concept is firmly established.[9] As predicted, combinations of SSRIs and selective and non-selective 5-HT_{1A} receptor antagonists elevate the extracellular 5-HT concentration in different brain areas more than the SSRIs alone.[17,40,68-70] In agreement with the greater self-inhibition of 5-HT release produced by SSRIs in serotonergic fibers that innervate the striatum or frontal cortex, 5-HT_{1A} receptor antagonists potentiate the effect of SSRIs to a large extent in these areas.[19,40,71,72] Smaller potentiations have been noted in dorsal or ventral hippocampus of freely-moving rats. Thus, the combination of paroxetine (3 mg/kg i.p.) and WAY-100635 (1 mg/kg s.c.) was 3.5-fold more effective in enhancing the extracellular 5-HT concentration in the striatum than in the dorsal hippocampus. In contrast, 5-HT_{1A} receptor antagonists potentiate the effects of SSRIs in the ventral hippocampus of anesthetized rats.[68] These differences are possibly accounted for by a distinct inhibitory tone on DRN serotonergic neurons during anesthesia. For instance, it has been shown that anesthetics block the excitatory effects of morphine on DRN neuones.[73]

In accordance with the potentiation of the extracellular 5-HT concentration induced by SSRIs, the administration of 5-HT_{1A} receptor antagonists synergistically augments the effects of SSRIs in behavioral models.[74-77]

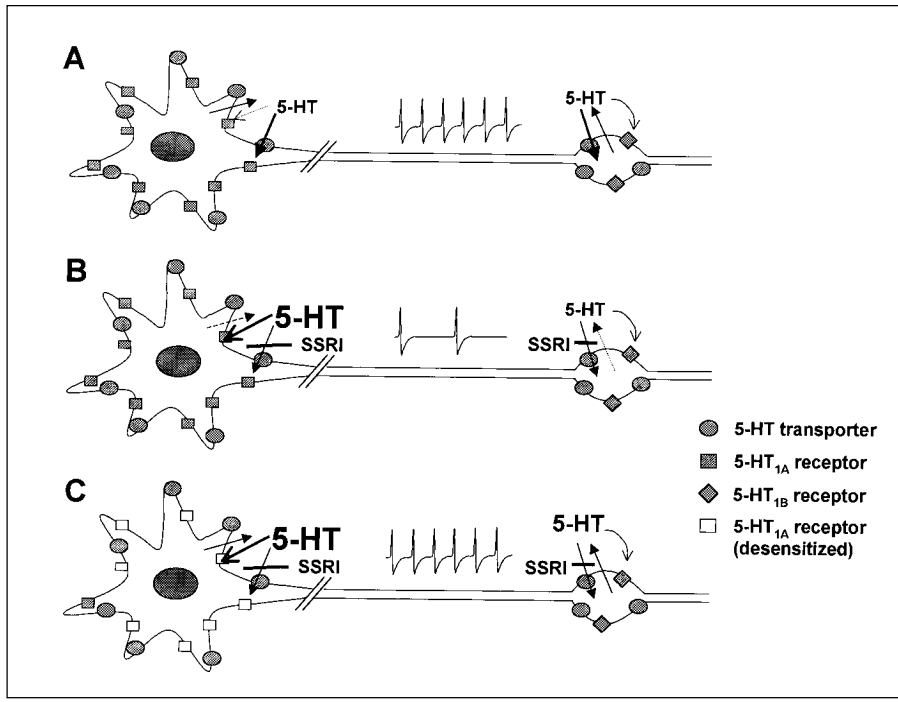

Fig. 9.5. Schematic representation of the effects of 5-HT reuptake inhibitors on serotonergic neurons. (A) 5-HT is released at the somatodendritic level and by proximal segments of serotonergic axons within the raphé nuclei and taken up by the 5-HT transporter. In these conditions there is little tonic activation of somatodendritic 5-HT_{1A} autoreceptors. At nerve terminals 5-HT_{1B} receptors control the 5-HT synthesis and release in a local manner. (B) The blockade of the 5-HT transporter at the level of the raphé nuclei elevates the concentration of extraneuronal 5-HT to an extent that activates somatodendritic autoreceptors (5-HT_{1A}). This leads to neuronal hyperpolatization, reduction of the discharge rate and reduction of 5-HT release by forebrain terminals. (C) The exposure to an enhanced extracellular 5-HT concentration produced by continuous treatment with SSRIs desensitizes raphé 5-HT_{1A} autoreceptors. The reduced 5-HT_{1A} function enables serotonergic neurons to recover cell firing and terminal release. Under these conditions, the SSRI-induced blockade of the 5-HT transporter in forebrain nerve terminals results in extracellular 5-HT increases larger than those observed after a single treatment with SSRIs.

SSRIs Plus Pindolol Combinations: Clinical Studies

Consistent with the inhibition of terminal 5-HT release produced by 5-HT reuptake inhibition in the midbrain raphé,[14] this group proposed that the use of 5-HT_{1A} receptor antagonists would accelerate and enhance the clinical effects of SSRIs.[67] An open-label study was published in 1994 which reported rapid antidepressant effects with the combination of paroxetine and pindolol (2.5 mg tid).[78] The latter agent was chosen for several reasons. First, no selective 5-HT_{1A} receptor antagonist was (and still is) available for human use. Secondly, of the various non-selective 5-HT_{1A} receptor antagonists available (mixed ß-adrenoceptor/5-HT_{1A} receptor antagonists such as pindolol, penbutolol, propanolol or

tertatolol), pindolol antagonizes 5-HT_{1A} receptor-mediated responses in humans.[79,80] Pindolol has been used subsequently by several other groups in open-label and placebo-controlled studies to examine whether it can accelerate the effects of SSRIs and other 5-HT-acting antidepressants.

Table 9.1 shows the open-label studies published at the time of writing. With the exception of one study, carried out in 13 melancholic, treatment-resistant patients, they all reported a beneficial effect of pindolol addition, either by accelerating the onset of the antidepressant action in drug-free patients or by eliciting a clinical response in treatment-resistant patients. Yet, a proper testing of this hypothesis at clinical level required evidence from double-blind placebo-controlled studies. Several such studies have now been reported in the form of an abstract published in 1997; these are listed in Table 9.2. In two of them, the addition of pindolol did not result in any acceleration or enhancement of the action of SSRIs. One of these studies was performed in treatment-resistant patients.[93]

The other four studies reported a significantly shorter time to onset of antidepressant response in the groups treated with the SSRI plus pindolol (compared with the SSRI plus placebo) and, in some instances, a higher response rate. In one of these studies, involving two different centers, the accelerating effect of pindolol was only observed in one of them,[91] a finding attributed to the different characteristics of the patients attending the two centers. Paroxetine was used in four studies and fluoxetine in two. Interestingly, the two studies involving the use of fluoxetine have yielded opposite results. Differences in patient characteristics, and particularly the existence of a larger percentage of chronic and comorbid patients in the study by Berman et al[88] may account for the distinct outcome in patients treated with SSRIs plus pindolol in this investigation when compared with results from other double-blind studies.

Mechanism of Action of Pindolol

We hypothesized that pindolol could accelerate and/or augment the effects of serotonergic antidepressants by preventing self-inhibition of cell firing and 5-HT release due to its ability to bind to 5-HT_{1A} receptors. Indeed, single doses of racemic pindolol (e.g., 30 mg) prevent the fall in body temperature and the changes in hormonal secretion induced by 5-HT_{1A} receptor agonists.[79,80] This shows that, at this dosage, pindolol has 5-HT_{1A} receptor antagonistic properties, despite reports of a partial agonistic character at ß-adrenoceptors and 5-HT_{1A} receptors when administered alone.[94,95] In binding assays using membrane preparations, the active isomer (-)pindolol displays a moderate affinity for rat 5-HT_{1A} receptors (p*K* approximately 7.5).[96] Yet, its affinity for 5-HT_{1A} receptors in human brain was unknown. We therefore carried out an autoradiographic study to determine the affinity of pindolol using [^{3}H]8-OH-DPAT (agonist) and [^{3}H]WAY 100635 (antagonist) as radioligands to label 5-HT_{1A} receptors. (-) Pindolol displaced in a monophasic way the binding of [^{3}H]8-OH-DPAT and [^{3}H]WAY-100635 from pre- and postsynaptic sites. The *K*i values for these sites were 7.6 and 3.8 nM for the rat brain and 10.7 and 6.5 nM for the human brain, respectively (Raurich et al, unpublished). Figure 9.6 shows the displacement of the [^{3}H]8-OH-DPAT binding at pre- and postsynaptic sites in rat and human brain by (-)pindolol.

Interestingly, the *K*i value of (-)pindolol for human 5-HT_{1A} receptors is below the plasma concentration of the racemic mixture found in the study by Pérez et al[89] which was approximately 25 nM (unpublished observations). This suggests that pindolol interacts with human 5-HT_{1A} receptors at the dose used in clinical studies (2.5 mg tid). However, other actions derived from its partial agonistic actions at ß-adrenoceptors cannot be excluded. The reduction of ß-adrenoceptor-mediated noradrenergic transmission was considered for years as a key event in antidepressant drug action, yet ß-adrenoceptor antagonists do not

Table 9.1. Uncontrolled studies on the use of pindolol to accelerate or enhance the antidepressant response in major depression

Artigas et al., 1994	78	Paroxetine; DF SSRIs, MAOIs, imipramine; TR	+ +
Blier and Bergeron, 1995	81	Paroxetine; DF SSRIs, MAOIs; TR	+ +
Dinan, et al., 1996	82	SSRIs, TR	-
Vinar et al., 1996	83	Citalopram, DF	+
Maes et al., 1996	84	Trazodone, DF	+
Bakish et al., 1997	85	Nefazodone, DF	+
Blier et al., 1997	86	Buspirone, Fluvoxamine Desipramine, Trimipramine; DF	+,-
Kraus et al., 1997	87	MAOI; TR	+

Abbreviations: DF, drug-free; MAOI, monoamine oxidase inhibitor; TR, treatment-resistant. The signs + and - refer to the overall conclusion expressed by the authors with respect to the accelerating/enhancing effect of pindolol.

possess any antidepressant activity. On the contrary, they appear to have a depressogenic action (in particular, propanolol).[97,98] Moreover, unlike some tricyclic antidepressants and monoamine oxidase inhibitors, most SSRIs do not down-regulate cortical β-adrenoceptors,[99,100] which suggests that this effect is not required for the establishment of a full antidepressant action. Furthermore, unlike pindolol, the addition of metoprolol (a β_1-adrenoceptor antagonist devoid of serotonergic properties) to paroxetine treatment did not result in a more rapid or effective antidepressant action[92] and pindolol did not produce a robust antidepressant effect when combined with desipramine or trimipramine, two antidepressants that do not interact with serotonergic neurons.[86] Taken together, these observations suggest that blockade of β-adrenoceptors by pindolol is unlikely to contribute to its acceleration of the effects of SSRIs.

In healthy subjects, pindolol (10 and 30 mg p.o.) reduces REM sleep,[101] a finding that has been interpreted as resulting from disinhibition of serotonergic firing activity produced by antagonism at raphé 5-HT_{1A} receptors.[92] This circumstantial evidence argues in favor of a serotonergic action of pindolol although additional actions through the noradrenergic system should not be overlooked, given its higher affinity for β-adrenoceptors.

It has been suggested that pindolol might selectively block presynaptic (somatodendritic) 5-HT_{1A} receptors.[40,68] This assumption was based on the observation that pindolol could

Table 9.2. Placebo-controlled studies of the use of pindolol to accelerate or enhance the antidepressant response in major depression*

Berman et al., 1997	88	Fluoxetine; DF (N=43)	-
Pérez et al., 1997	89	Fluoxetine; DF (N=111)	+
Thomas et al., 1997	90	Paroxetine; DF (N=100)	+
Tomé et al., 1997	91	Paroxetine; DF (N=80)	+,-[(1)]
Zanardi et al., 1997	92	Paroxetine; DF (N=63)	+
Moreno et al.,1997	93	SSRIs; TR (N=10)	-

Abbreviations; DF, drug-free; TR, treatment-resistant. The signs + and - refer to the overall conclusion expressed by the authors with respect to the effect of pindolol.
(1) study conducted in two centers, with positive results in one of them.
* Since the time of writing, several more placebo controlled studies have appeared in the literature.[93a-93d] Overall, they support the effectiveness of pindolol to accelerate the effects of SSRIs in untreated patients whereas controversial results have been obtained in treatment-resistant patients.

block the suppression of cell firing in the DRN produced by the intravenous administration of paroxetine but not the inhibition of hippocampal CA3 pyramidal neurons elicited by the microiontophoretic administration of 5-HT or 8-OH-DPAT. In both cases, pindolol was administered subcutaneously by mini-pumps. However, since pindolol is a competitive antagonist, it might not have blocked the effects of the microiontophoretic application of agonists due to a larger focal concentration at 5-HT_{1A} receptors produced by this procedure, compared with the more moderate increments of 5-HT produced in the DRN by the subcutaneous administration of paroxetine. A recent report supports this view by showing that the hyperpolarization of DRN and CA1 hippocampal pyramidal neurons induced by the non-selective 5-HT_{1A} receptor agonist 5-carboxyamidotryptamine is competitively antagonized by (-)pindolol in brain slices.[102] The latter data are in full agreement with the inhibition of [^{3}H]8-OH-DPAT binding to pre- and postsynaptic 5-HT_{1A} receptors by (-)pindolol shown in Figure 9.6.

Future Perspectives

Given the current lack of selective 5-HT_{1A}-receptor antagonists available for human use, it seems that the final testing of the above hypothesis will have to wait until such compounds have been developed. The current lack of selectivity and limited number of 5-HT_{1A} receptor antagonists leaves open several important questions. Furthermore, it is unknown whether other mixed β-adrenoceptor/5-HT_{1A} receptor ligands, such as penbutolol or tertatolol would be effective when used in combination with SSRIs. Also, it has not been established whether the action of pindolol is exerted exclusively via 5-HT_{1A} receptors. Indeed,

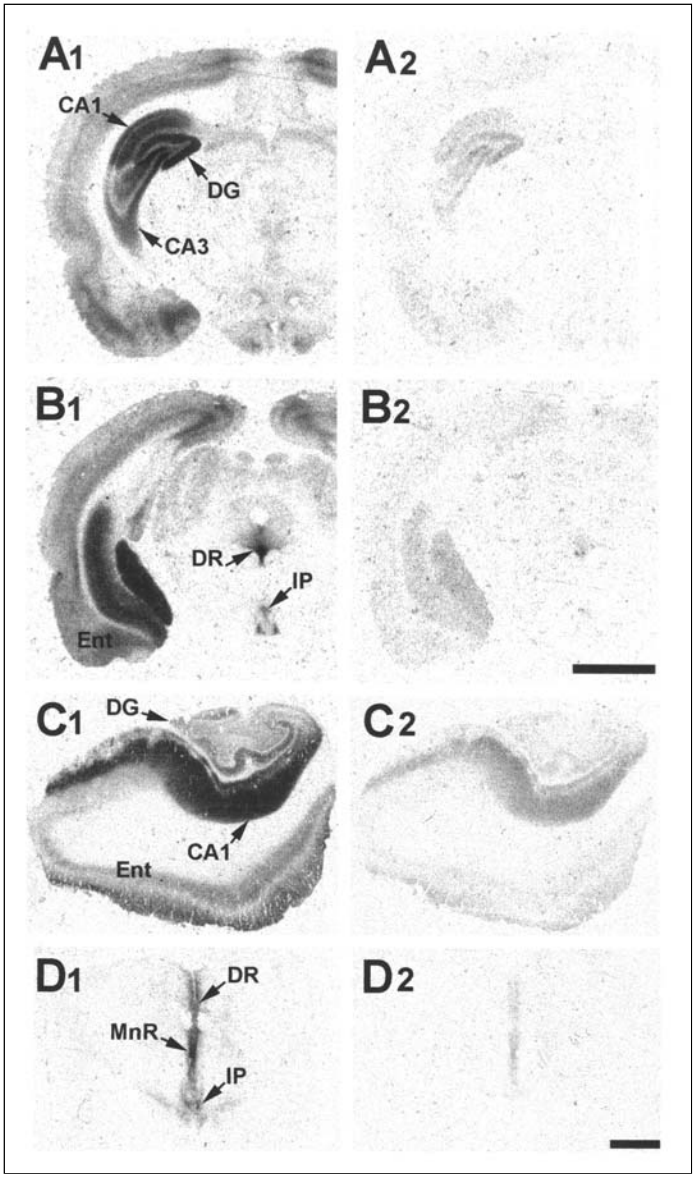

Fig. 9.6. Autoradiographic images showing the labelling of 5-HT_{1A} receptors with [^{3}H]8-OH-DPAT in rat (A1-B2) and human (C1-D2) brain sections through the hippocampus and dorsal raphé. (A1-D1) Total binding of [^{3}H]8-OH-DPAT (0.49 nM). (A2-D2) The addition of (-)pindolol (10^{-7} M) to the incubation medium strongly inhibits binding of the radioligand to 5-HT_{1A} receptors. The effects of (-)pindolol are comparable among regions and across species. Abbreviations: CA1, CA1 hippocampal field; CA3, CA3 hippocampal field; DG, dentate gyrus; DR, dorsal raphé nucleus; Ent, entorhinal cortex; IP, interpeducular nucleus; MnR, median raphé nuclus. Bars: 3 mm (A=B, C=D).

this issue has important consequences in terms of drug development. Finally, it is uncertain whether a putative blockade of postsynaptic 5-HT_{1A} receptors would diminish the benefits of enhancing the presynaptic serotonergic function. It has been suggested that an enhanced transmission through hippocampal 5-HT_{1A} receptors could be the common pathway by which a variety of antidepressant drugs, including SSRIs, monoamine oxidase inhibitors, tricyclic drugs and even drugs with a primary noradrenergic action, exert their antidepressant effects.[13,59] This hypothesis could be easily tested by the administration of a selective 5-HT_{1A} receptor antagonist able to block pre-and postsynaptic receptors. This should provoke a rapid relapse of recovered patients treated with different antidepressant drugs. However, it seems likely that other 5-HT receptors and brain areas are involved in the action of antidepressants, given the large number of 5-HT receptors and the anatomical evidence that cortical areas are involved in the pathophysiology of depression.[103,104] Research of the mode of action of SSRIs should establish the 5-HT receptor subtypes and brain areas involved in their action using complementary experimental models in animals and humans. Non-invasive imaging techniques, such as PET scanning, are likely to provide a more complete view of the actions of SSRIs than any other methodology used so far. More specifically, this technique will undoubtedly help to establish the relationship between 5-HT_{1A} receptor occupancy and therapeutic action of SSRIs which appears to be crucial for the development of new and more effective antidepressant drugs.

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References

1. Blakely RD, Berson HE, Fremeau RT et al. Cloning and expression of a functional serotonin transporter from rat brain. Nature 1991; 354:66-70.
2. Hoffman BJ, Mezey E, Brownstein M. Cloning of a serotonin transporter affected by antidepressants. Science 1991; 249:1303-1306.
3. Uhl GR, Hartig PR. Transporter explosion: Update on uptake. Trends Pharmacol Sci 1992; 13:421-425.
4. Bolden-Watson C, Richelson E. Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes. Life Sci 1993; 52:1023-1029.
5. Hyttel J. Pharmacological characterization of selective serotonin reuptake inhibitors (SSRIs). Int Clin Psychopharmacol 1994; 9:19-26.
6. Richelson E, Nelson A. Antagonism by antidepressants of neurotransmitter receptors of normal human brain in vitro. J Pharmacol Exp Ther 1984; 230:94-102.
7. Lesch KP, Wolozin BL, Estler HC et al. Isolation of a cDNA encoding the human brain serotonin transporter. J Neural Transm 1993; 91:67-72.
8. Lesch KP, Wolozin BL, Murphy DL et al. Primary structure of the human platelet serotonin uptake site—Identity with the brain serotonin transporter. J Neurochem 1993; 60:2319-2322.
9. Artigas F, Romero L, de Montigny C et al. Acceleration of the effect of selected antidepressant drugs in major depression by 5-HT_{1A} antagonists. Trends Neurosci 1996; 19:378-383.
10. Scuvée-Moreau J, Dresse A. Effect of various antidepressant drugs on the spontaneous firing rate of locus coeruleus and dorsal raphe neurons of the rat. Eur J Pharmacol 1979; 57:219-225.
11. Quinaux N, Scuvée-Moreau J, Dresse A. Inhibition of in vitro and ex vivo uptake of noradrenaline and 5-hydroxytryptamine by five antidepressants; correlation with reduction

of spontaneous firing rate of central monoaminergic neurones. Naunyn-Schmiedeberg's Arch Pharmacol 1982; 319:66-70.
12. Blier P, de Montigny C. Electrophysiological investigations on the effect of repeated zimeldine administration on serotonergic neurotransmission in the rat. J Neurosci 1983; 3:1270-1278.
13. Blier P, de Montigny C, Chaput Y. Modifications of the serotonin system by antidepressant treatment: Implications for the therapeutic response in major depression. J Clin Psychopharmacol 1987; 7:24S-35S.
14. Adell A, Artigas F. Differential effects of clomipramine given locally or systemically on extracellular 5-hydroxytryptamine in raphe nuclei and frontal cortex. An in vivo microdialysis study. Naunyn-Schmiedeberg's Arch Pharmacol 1991; 343:237-244.
15. Bel N, Artigas F. Fluvoxamine preferentially increases extracellular 5-hydroxytryptamine in the raphe nuclei: An in vivo microdialysis study. Eur J Pharmacol 1992; 229:101-103.
16. Invernizzi R, Belli S, Samanin R. Citalopram's ability to increase the extracellular concentration of serotonin in the dorsal raphe prevents the drug's effect in frontal cortex. Brain Res 1992; 584:322-324.
17. Gartside SE, Umbers V, Hajos M et al. Interaction between a selective 5-HT_{1A} receptor antagonist and an SSRI in vivo: Effects on 5-HT cell firing and extracellular 5-HT. Br J Pharmacol 1995; 115:1064-1070.
18. Malagié I, Trillat AC, Jacquot C et al.. Effects of acute fluoxetine on extracellular serotonin levels in the raphe: An in vivo microdialysis study. Eur J Pharmacol 1996; 286:213-217.
19. Romero L, Artigas F. Preferential potentiation of the effects of serotonin uptake inhibitors by 5-HT_{1A} receptor antagonists in the dorsal raphe pathway: Role of somatodendritic autoreceptors. J Neurochem 1997; 68:2593-2603.
20. Cortés R, Soriano E, Pazos A et al.. Autoradiography of antidepressant binding sites in the human brain: Localization using [^{3}H]imipramine and [^{3}H]paroxetine. Neurosci 1988; 27:473-496.
21. Hrdina PD, Foy B, Hepner A et al. Antidepressant binding sites in brain: Autoradiographic comparison of [^{3}H]paroxetine and [^{3}H]imipramine, localization and relationship to serotonin transporter. J Pharmacol Exp Ther 1990; 252:410-418.
22. Héry F, Faudon M, Ternaux JP. In vivo release of serotonin in two raphe nuclei (raphe dorsalis and magnus) of the cat. Brain Res Bull 1982; 8:123-129.
23. Adell A, Carceller A, Artigas F. In vivo brain dialysis study of the somatodendritic release of serotonin in the raphe nuclei of the rat. Effects of 8-hydroxy-2-(di-n-propylamino)tetralin. J Neurochem 1993; 60:1673-1681.
24. Bosker F, Klompmakers A, Westenberg H. Extracellular 5-hydroxytryptamine in median raphe nucleus of the conscious rat is decreased by nanomolar concentrations of 8-hydroxy-2-(di-n-propylamino)tetralin and is sensitive to tetrodotoxin. J Neurochem 1994; 63:2165-2171.
25. Matos FF, Urban C, Yocca FD. Serotonin (5-HT) release in the dorsal raphé and ventral hippocampus: raphé control of somatodendritic and terminal 5-HT release. J Neural Transm 1996; 103:173-190.
26. Halliday G, Harding A, Paxinos G. Serotonin and Tachykinin Systems. In: Paxinos G, ed. The Rat Nervous System, 2nd ed. Sydney: Academic Press, 1995:929-974.
27. a) Hervás I, Artigas F. Effect of fluoxetine on extracellular 5-hydroxytryptamine in the rate brain. Role of 5-HT autoreceptors. Eur J Pharmacol 1998; 358:9-18.
27. b) Paxinos G, Watson C. The Rat Brain in Stereotaxic Coordinates. Compact Third Edition. Orlando; Academic Press 1997.
28. Pazos A, Palacios JM. Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors. Brain Res 1985; 346:205-230.
29. Sotelo C, Cholley B, El Mestikawy S et al. Direct immunohistochemical evidence of the existence of 5-HT autoreceptors on serotonergic neurons in the midbrain raphe nuclei. Eur J Neurosci 1990; 2:1144-1154.

30. Pompeiano M, Palacios JM, Mengod G. Distribution and cellular localization of mRNA coding for 5-HT_{1A} receptor in the rat brain: Correlation with receptor binding. J Neurosci 1992; 12:440-453.
31. Andrade R, Malenka RC, Nicoll RA. A G protein couples serotonin and $GABA_B$ receptors to the same channel in hippocampus. Science 1986; 234:1261-1265.
32. Innis RB, Aghajanian GK. Pertussis toxin blocks 5-HT_{1A} and $GABA_B$ receptor-mediated inhibition of serotonergic neurons. Eur J Pharmacol 1987; 143:195-204.
33. De Vivo M, Maayani S. Characterization of the 5-hydroxytryptamine 1A receptor-mediated inhibition of forskolin-stimulated adenylate cyclase activity in guinea-pig and rat hippocampal membranes. J Pharmacol Exp Ther 1986; 238:248-253.
34. Markstein R, Hoyer D, Engel G. 5-HT_{1A}-receptors mediate stimulation of adenylate cyclase in rat hippocampus. Naunyn-Schmiedeberg's Arch Pharmacol 1986; 333:335-341.
35. Clarke WP, Yocca FD, Maayani S. Lack of 5-hydroxytryptamine(1A)- mediated inhibition of adenylyl cyclase in dorsal raphe of male and female rats. J Pharmacol Exp Ther 1996; 277:1259-1266
36. Hutson PH, Sarna GS, O'Connell MT et al. Hippocampal 5-HT synthesis and release in vivo is decreased by infusion of 8-OH-DPAT into the nucleus raphe dorsalis. Neurosci Lett 1989; 100:276-280.
37. Invernizzi R, Carli M, Di Clemente A et al. Administration of 8-hydroxy-2-(di-n-propyl-amino)tetralin in raphe nuclei dorsalis and medianus reduces serotonin synthesis in the rat brain: differences in potency and regional sensitivity. J Neurochem 1991; 56:243-247.
38. Romero L, Casanovas JM, Hervás I et al. Strategies to optimize the antidepressant action of selective serotonin reuptake inhibitors. In: Skolnick P, ed. Antidepressants: Current Trends and Future Directions, Totowa; New Jersey: Humana Press, 1997:1-33.
39. Romero L, Celada P, Artigas F. Reduction of in vivo striatal 5-hydroxytryptamine release by 8-OH-DPAT after inactivation of Gi/Go proteins in dorsal raphe nucleus. Eur J Pharmacol 1994; 265:103-106.
40. Romero L, Bel N, Artigas F et al. Effect of pindolol on the function of pre- and postsynaptic 5-HT_{1A} receptors: In vivo microdialysis and electrophysiological studies in the rat brain. Neuropsychopharmacol 1996; 15:349-360.
41. Blier P, de Montigny C. Current advances and trends in the treatment of depression. Trends Pharmacol Sci 1994; 15:220-226.
42. Arborelius L, Nomikos GG, Grillner P et al. 5-HT_{1A} receptor antagonists increase the activity of serotonergic cells in the dorsal raphe nucleus in rats treated acutely or chronically with citalopram. Naunyn-Schmiedeberg's Arch Pharmacol 1995; 352:157-165.
43. Azmitia EC, Segal M. An autoradiographic analysis of the differential ascending projections of the dorsal and median raphe nuclei in the rat. J Comp Neurol 1978; 179:641-668.
44. McQuade R, Sharp T. Functional mapping of dorsal and median raphe 5-hydroxytryptamine pathways in forebrain of the rat using microdialysis. J Neurochem 1997; 69:791-796.
45. Casanovas JM, Artigas F. Differential effects of ipsapirone on 5-HT release in the dorsal and median raphe neuronal pathways. J Neurochem 1996; 67:1945-1952.
46. Casanovas JM, Lésourd M, Artigas F. The selective 5-HT_{1A} agonists alnespirone (S-20499) and 8-OH-DPAT reduce extracellular 5-hydroxytryptamine in rat brain in a regionally-selective manner. Br J Pharmacol 1997; 122:733-741.
47. Rutter JJ, Auerbach SB. Acute uptake inhibition increases extracellular serotonin in the rat forebrain. J Pharmacol Exp Ther 1993; 265:1319-1324.
48. Hjorth S, Auerbach SB. Further evidence for the importance of 5-HT_{1A} autoreceptors in the action of selective serotonin reuptake inhibitors. Eur J Pharmacol 1994; 260:251-255.
49. Auerbach SB, Lundberg JF, Hjorth S. Differential inhibition of serotonin release by 5-HT and NA reuptake blockers after systemic administration. Neuropharmacol 1995; 34:89-96.
50. Hjorth S, Auerbach SB. 5-HT_{1A} autoreceptors and the mode of action of selective serotonin reuptake inhibitors (SSRI). Behav Brain Res 1996; 73:281-283.
51. Sinton CM, Fallon SL. Electrophysiological evidence for a functional differentiation between subtypes of the 5-HT1 receptor. Eur J Pharmacol 1988; 157:173-181.

52. Hajos M, Gartside SE, Sharp T. Inhibition of median and dorsal raphe neurones following administration of the selective serotonin reuptake inhibitor paroxetine. Naunyn-Schmiedeberg's Arch Pharmacol 1995; 351:624-629.
53. Kreiss DS, Lucki I. Differential regulation of 5-HT release in the striatum and hippocampus by 5-HT_{1A} autoreceptors of the dorsal and median raphe nuclei. J Pharmacol Exp Ther 1994; 269:1268-1279.
54. Starke K, Göthert M, Kilbinger H. Modulation of neurotransmitter release by presynaptic autoreceptors. Physiol Rev 1989; 69:864-989.
55. Middlemiss DN. Stereoselective blockade at [^{3}H]5-HT binding sites and at the 5-HT autoreceptor by propranolol. Eur J Pharmacol 1984; 101:289-293.
56. Moret C, Briley M. 5-HT autoreceptors in the regulation of 5-HT release from guinea pig raphe nucleus and hypothalamus. Neuropharmacology 1997; 36:1713-1723
57. Davidson C, Stamford JA. Serotonin efflux in the rat ventral lateral geniculate nucleus assessed by fast cyclic voltammetry is modulated by 5-HT_{1B} and 5-HT_{1D} autoreceptors. Neuropharmacology 1996; 35:1627-1634.
58. Trillat AC, Malagié I, Scearce K et al. Regulation of serotonin release in the frontal cortex and ventral hippocampus of homozygous mice lacking 5-HT_{1B} receptors: In vivo microdialysis studies. J Neurochem 1997; 69:2019-2025.
59. Goodwin GM, de Souza RJ, Green AR. Presynaptic serotonin receptor-mediated response in mice attenuated by antidepressant drugs and electroconvulsive shock. Nature 1985; 317:531-533.
60. Hensler JG, Covachich A, Frazer A. A quantitative autoradiographic study of serotonin 1A receptor regulation. Effect of 5,7-dihydroxytryptamine and antidepressant treatments. Neuropsychopharmacology 1991; 4:131-144.
61. Bel N, Artigas F. Chronic treatment with fluvoxamine increases extracellular serotonin in frontal cortex but not in raphe nuclei. Synapse 1993; 15:243-245.
62. Bosker FJ, Vanesseveldt KE, Klompmakers AA et al. Chronic treatment with fluvoxamine by osmotic minipumps fails to induce persistent functional changes in central 5-HT(1A) and 5-HT(1B) receptors, as measured by in vivo microdialysis in dorsal hippocampus of conscious rats. Psychopharmacol 1995; 117:358-363.
63. Invernizzi R, Bramante M, Samanin R. Chronic treatment with citalopram facilitates the effect of a challenge dose on cortical serotonin output: Role of presynaptic 5-HT_{1A} receptors. Eur J Pharmacol 1994; 260:243-246.
64. Invernizzi R, Bramante M, Samanin R. Extracellular concentrations of serotonin in the dorsal hippocampus after acute and chronic treatment with citalopram. Brain Res 1995; 696:62-66.
65. Rutter JJ, Gundlah C, Auerbach SB. Increase in extracellular serotonin produced by uptake inhibitors is enhanced after chronic treatment with fluoxetine. Neurosci Lett 1994; 171:183-186.
66. Arborelius L, Nomikos GG, Hertel P et al. The 5-HT_{1A} receptor antagonist (S)-UH-301 augments the increase in extracellular concentrations of 5-HT in the frontal cortex produced by both acute and chronic treatment with citalopram. Naunyn-Schmiedeberg's Arch Pharmacol 1996; 353:630-640.
67. Artigas F. 5-HT and antidepressants: New views from microdialysis studies. Trends Pharmacol Sci 1993; 14:262.
68. Hjorth S. Serotonin 5-HT_{1A} autoreceptor blockade potentiates the ability of the 5-HT reuptake inhibitor citalopram to increase nerve terminal output of 5-HT in vivo: A microdialysis study. J Neurochem 1993; 60:776-779.
69. Dreshfield LJ, Wong DT, Perry KW et al. Enhancement of fluoxetine-dependent increase of extracellular serotonin (5-HT) levels by (-)-pindolol, an antagonist at 5-HT_{1A} receptors. Neurochem Res 1996; 21:557-562.
70. Romero L, Hervás I, Artigas F. The 5-HT_{1A} antagonist WAY 100635 selectively potentiates the presynaptic effects of serotonergic antidepressants in rat brain. Neurosci Lett 1996; 219:123-126.

71. Invernizzi R, Velasco C, Bramante M et al. Effect of 5-HT_{1A} receptor antagonists on citalopram-induced increase in extracellular serotonin in the frontal cortex, striatum and dorsal hippocampus. Neuropharmacology 1997; 36:467-473.
72. Malagié I, Trillat AC, Douvier E et al. Regional differences in the effect of the combined treatment of WAY 100635 and fluoxetine. An in vivo microdialysis study. Naunyn-Schmiedeberg's Arch Pharmacol 1996; 354:785-790.
73. Tao R, Auerbach SB. Anesthetics block morphine-induced increases in serotonin release in rat CNS. Synapse 1994; 18:307-314.
74. Sánchez C. Interaction studies of 5-HT_{1A} receptor antagonists with selective 5-HT reuptake inhibitors in isolated aggressive mice. Eur J Pharmacol 1997; 334:127-132.
75. Zhou FC, McKinzie DL, Patel TD et al. Additive reduction of alcohol drinking by 5-HT_{1A} antagonist WAY 100635 and serotonin uptake blocker fluoxetine in alcohol-preferring rats. Alcohol Clin Exp Res 1998; 22:266-269
76. Hashimoto S, Inoue T, Koyama T. Effects of the coadministration of 5-HT_{1A} receptor antagonists with an SSRI in conditioned fear stress-induced freezing behavior. Pharmacol Biochem Behav 1997; 58:471-475.
77. Li DL, Simmons RMA, Iyengar S. 5-HT(1A) receptor antagonists enhance the functional activity of fluoxetine in a mouse model of feeding. Brain Res 1998; 781:91-99
78. Artigas F, Perez V, Alvarez E. Pindolol induces a rapid improvement of depressed patients treated with serotonin reuptake inhibitors. Arch Gen Psychiatry 1994; 51:248-251.
79. Lesch KP, Poten B, Sohnle K et al. Pharmacology of the hypothermic response to 5-HT_{1A} receptor activation in humans. Eur J Clin Pharmacol 1990; 39:17-19.
80. Meltzer HY, Maes M. Effect of pindolol on the L-5-HTP-induced increase in plasma prolactin and cortisol concentrations in man. Psychopharmacology 1994; 114:635-643.
81. Blier P, Bergeron R. Effectiveness of pindolol with selected antidepressant drugs in the treatment of major depression. J Clin Psychopharmacol 1995; 15:217-222.
82. Dinan TG, Scott JV. Does pindolol induce a rapid improvement in depressed patients resistant to serotonin reuptake inhibitors. J Serotonin Res 1996; 3:119-121.
83. Vinar O, Vinarova E, Horacek J. Pindolol accelerates the therapeutic action of selective serotonin reuptake inhibitors (SSRI) in depression. Homeostasis 1996; 37:93-95.
84. Maes M, Vandoolaeghe E, Desnyder R. Efficacy of treatment with trazodone in combination with pindolol or fluoxetine in major depression. J Affective Disord 1996; 41:201-210.
85. Bakish D, Hooper CL, Thornton MD et al. Fast onset: An open study of the treatment of major depressive disorder with nefazodone and pindolol combination therapy. Int Clin Psychopharmacol 1997; 12:91-97.
86. Blier P, Bergeron R, de Montigny C. Selective activation of postsynaptic 5-HT_{1A} receptors induces rapid antidepressant response. Neuropsychopharmacol 1997; 16:333-338.
87. Kraus RP. Pindolol augmentation of tranylcypromine in psychotic depression. J Clin Psychopharmacol 1997; 17:225-226.
88. Berman RM, Darnell AM, Miller HL et al. Effect of pindolol in hastening response to fluoxetine in the treatment of major depression: A double-blind, placebo-controlled trial. Am J Psychiatry 1997;154:37-43.
89. Pérez V, Gilaberte I, Faries D et al. Randomised, double-blind, placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment The Lancet 1997; 349:1594-1597.
90. Thomas P, Bordet R, Alexandre JY et al. Pindolol addition shortens delay of action of paroxetine in major depression: A double blind controlled study. Eur Neuropsychopharmacol 1997; 7(Suppl 2):S173.
91. Tomé MB, Isaac MT, Harte R et al. Paroxetine and pindolol: A randomized trial of serotonergic autoreceptor blockade in the reduction of antidepressant latency. Int Clin Psychopharmacol 1997; 12:81-89.
92. Zanardi R, Artigas F, Franchini L et al. How long should pindolol be associated with paroxetine to improve the antidepressant response? J Clin Psychopharmacol 1997; 17:446-450.

93. Moreno FA, Gelenberg AJ, Bachar K et al. Pindolol augmentation of treatment-resistant depressed patients. J Clin Psychiatry 1997; 58:437-439.
93. a) Zanardi R, Franchini L, Gasperinin M et al. Faster onset of action of fluvoxamine in combination with pindolol in the treatment of delusional depression: A controlled study. J Clin Psychopharmacol 1998; 18:441-446.
93. b) Bordet R, Thomas P, Dupuis B et al. Reseau de Recherche et d'Experimentation Psychopharmacologique. effect of pindolol on onset of action of paroxetine in the treatment of major depression: Intermediate analysis of a double-blind; placebo-controlled trail. Am J Psychiatry 1998; 155:1346-1351.
93. c) Maes M, LIbbrecht I, van Hunsel et al. Pindolol and mianserin augment the antidepressant activity of fluoxetine in hospitalized major depressed patients, including those with treatment resistance. J Clin Psychopharmacol 1999; 19:177-182.
93. d) Pérez V, Soler j, Puigdemon D et al. Grup de Recerca en Trastoms Afectius. A double-blind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. Arch Gen Psychiatry 1999; 56:375-379.
94. Frishman WH. Pindolol: A new beta-adrenoceptor antagonist with partial agonist activity. New Eng J Med 1983; 308 (16):941-944.
95. Meltzer HY, Maes M. Effect of pindolol on hormone secretion and body temperature: Partial agonist effects. J Neural Transm 1996; 103:77-88.
96. Hoyer D, Schoeffter P. 5-HT receptors: Subtypes and second messengers. J Receptor Res 1991;11:197-214.
97. Avorn J, Everitt DE, Weiss D. Increased antidepressant use in patients prescribed beta-blockers. JAMA 1986; 255:357-360.
98. Thiessen BQ, Walace SM, Blackburn JL. Increased prescribing of antidepressants subsequent to ß-blocker therapy. Arch Intern Med 1990; 150:2286-2290.
99. Peroutka SJ, Snyder SH. Long-term antidepressant treatment decreases spiroperidol-labeled serotonin receptor binding. Science 1980; 210:88-90.
100. Palvimaki EP, Laakso A, Kuoppamaki M et al. Up-regulation of beta(1)-adrenergic receptors in rat brain after chronic citalopram and fluoxetine treatments. Psychopharmacology 1994; 115:543-546.
101. Seifritz E, Stahl SM, Gillin JC. Human sleep EEG following the 5-HT_{1A} antagonist pindolol: Possible disinhibition of raphe neuron activity. Brain Res 1997; 759:84-91
102. Corradetti R, Laaris N, Hamoun N et al. Antagonist properties of (-)pindolol and WAY 100635 at somatodendritic and postsynaptic 5-HT_{1A} receptors in the rat brain. Br J Pharmacol 1998; 123:449-452.
103. Drevets WC, Price JL, Simpson JR et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 1997; 386:824-827.
104. Biver F, Wikler D, Lostra F et al. Serotonin 5-HT_2 receptor imaging in major depression: Focal changes in orbito-insular cortex. Br J Psychiatry 1997; 171:444-448.

CHAPTER 10

SSRI-Induced Changes in Catecholaminergic Transmission

S. Clare Stanford

The selective serotonin reuptake inhibitors (SSRIs) are a chemically diverse group of compounds which share the characteristic of potently inhibiting neuronal reuptake of serotonin (5-hydroxytryptamine, 5-HT). As their name suggests, the antidepressant effects of SSRIs are widely attributed to their preferential inhibition of 5-HT reuptake rather than that of other endogenous monoamines (noradrenaline and dopamine). However, it has been obvious for some time that the apparent selectivity of SSRIs for inhibition of 5-HT uptake in vivo is much lower than would be predicted from in vitro measurements. Yet, their effects on noradrenergic and dopaminergic neurons have attracted detailed attention only relatively recently. These actions are the focus of this chapter, which will consider whether direct or indirect effects of SSRIs on catecholamine-releasing neurons could contribute to their antidepressant actions.

SSRIs and Extracellular Catecholamines

One test of whether changes in catecholaminergic transmission could contribute to the therapeutic effects of SSRIs is to establish that these drugs increase the concentration of extracellular catecholamines in the brain. Although the development of microdialysis in vivo has enabled investigation of this question, the few studies that have been carried out differ in respect of the brain region studied, the compounds tested, the dose administered and the route by which the drug is given. Nevertheless, with the exception of fluvoxamine, published reports generally agree that there is an increase in the concentration of extracellular noradrenaline and dopamine after either local infusion (via the microdialysis probe) or systemic administration of an SSRI (Table 10.1). Despite the dearth of studies from which to form any firm conclusions, it seems that there could be regional variation in the effects of individual compounds. This could well reflect regional differences in the density of monoamine transporters or the spontaneous (resting tonic) release of catecholamines.

There is reason to believe that inhibition of neuronal reuptake of noradrenaline could contribute to the SSRI-induced increase in the extracellular concentration of this neurotransmitter, especially when test drugs are perfused via the probe. For instance, an appreciable increase in the concentration of extracellular noradrenaline is achieved on infusion of 5 μM of fluoxetine.[14] Bearing in mind that probably as little as 10% of the test compound diffuses from the probe, and that its concentration will decline progressively with increasing distance from the probe, the highest concentration of fluoxetine in the extracellular fluid will be close to its K_i for inhibition of noradrenaline reuptake (0.1-10 μM) (see: Table 10.3). Evidence described below confirms that such concentrations of fluoxetine are also well within the range of those attained in the clinical context. In general, K_is for

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Table 10.1. Effects of SSRIs on catecholamine efflux in rat brain

		Noradrenaline		Dopamine	
	Brain region	**Efflux**	**Reference**	**Efflux**	**Reference**
Local infusion					
Citalopram	frontal cortex	↑	1		
	ventral tegmentum	↑	2	↑	2
Fluoxetine	frontal cortex	↑	1,3	↑	3
	hypothalamus	NC	4		
	striatum			↑	9
	ventral tegmentum			↑	2
Fluvoxamine	frontal cortex	NC	3	↑	3
Paroxetine	hippocampus	NC	5		
Systemic					
Citalopram	ventral tegmentum			↑ (weak)	10
Fluoxetine	frontal cortex	↑	3,6	↑	3,6
	hypothalamus	↑	4,7		
	straitum			NC	11,12
				↓	13
	nucleus accumbens			↓	13
	ventral tegmentum			↑	10
Fluvoxamine	frontal cortex	NC	3	NC	3
Paroxetine	hippocampus	↑	8		

↑; increase, ↓; decrease, NC; no change

inhibition of dopamine uptake are higher than those for noradrenaline and so it is less likely that therapeutic doses of SSRIs will affect reuptake of this neurotransmitter. However, one limitation of microdialysis is that it is hard to distinguish whether an increase in the extracellular concentration of a neurotransmitter is due to a reduction in its rate of reuptake and/or an increase in its rate of release. These alternatives are discussed in the following sections.

Monoamine Transporters

Neuronal uptake of monoamines is effected by a subfamily of membrane glycoproteins that have extensive amino acid sequence homology (Fig. 10.1). Early studies established that cotransport of Na^+ ions is essential for neuronal uptake of noradrenaline[15] and this has

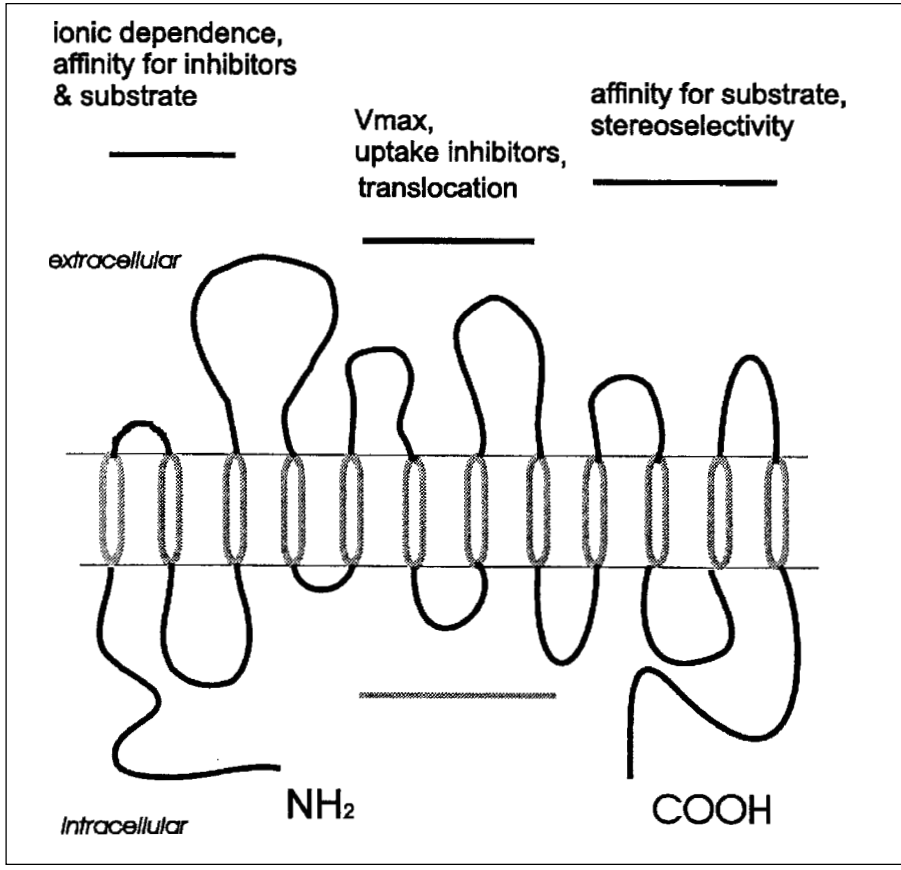

Fig. 10.1. Schematic diagram of the catecholamine transporters showing the 12 transmembrane, hydrophobic domains and the -NH_2 and -COOH termini. Targets for specific binding ligands are thought to be within regions indicated by the solid bars. Based on refs. 18, 30, and 34.

now been confirmed for 5-HT and dopamine transporters as well. Uptake of all these monoamines is influenced by the concentration of Cl^- ions in the external medium and stimulated by intraneuronal K^+ (or H^+) ions. In view of all these common features, it would not be at all surprising if the different monoamine transporters showed some degree of functional overlap.

It is envisaged that monoamine transporters exist in two interchangeable states which differ in the extent to which they bind ions and substrate. A conformational change in the transporter is thought to be triggered by the binding of Na^+ and monoamine to its extracellular surface. By analogy with ion channels, this is thought to result in the sequential opening of outer and inner channel 'gates' which enables translocation of bound ligands from the extracellular space towards the neuronal cytosol. For 5-HT transporters at least, this process is coupled to outward transport of intraneuronal K^+. Under certain circumstances, notably during ischemia[16] or after treatment with amphetamines,[17] the transport of

monoamines is reversed, resulting in their extrusion from the neuron; retrotransport of dopamine is discussed again later.

Recent reviews have detailed the molecular structure and distribution of the monoamine transporters,[18] as well as their regulation by second messenger systems,[19] their ligand interactions and transport kinetics.[20] However, in the context of this chapter, it is both their substrate selectivity and inhibitor sensitivity which is of greatest interest. This is because any inhibition of the reuptake of catecholamines by an SSRI could be explained in two ways. One is that the transporter proteins for each of the monoamines are not especially substrate selective so that the SSRIs acting at the 5-HT transporter can prevent reuptake of catecholamines as well as that of 5-HT. Alternatively, it is the SSRIs which lack selectivity in vivo such that they can prevent reuptake of catecholamines by their respective transporters.

Substrate Selectivity and Inhibitor Sensitivity of Cloned Transporters

Studies of the cloned human 5-HT transporter expressed in HeLa cells indicate that the K_is for inhibition of [^{3}H]5-HT uptake by dopamine and noradrenaline are approximately 20-fold greater than the K_M for 5-HT.[21] However, one complication is that three mRNA transcripts (8.2, 5.0 and 3.3 kb) have been identified in human post-mortem brain tissue, all of which hybridize to the cDNA probe for the 5-HT transporter. Although these mRNAs are thought to be derived from a single gene, there is some tissue specificity in their distribution.[22] This could mean that different mRNAs yield translation products which differ in their substrate selectivity and/or inhibitor sensitivity. This is rendered all the more plausible by evidence that even single point mutations of the 5-HT transporter markedly affect both the kinetics of 5-HT uptake and the affinity of uptake inhibitors.[23,24] It has even been suggested that abnormal populations of 5-HT transporters could underlie some psychiatric and neurological disorders.[22,25]

In contrast, noradrenaline and dopamine transporters show poor selectivity for their respective substrates, a feature which is entirely consistent with their approximately 75% amino acid sequence homology. In fact, dopamine seems to be the preferred substrate for noradrenaline transporters in human placental brush border membranes[26] and cloned human noradrenaline transporters expressed in HeLa cells.[27] Studies of cloned human noradrenaline and rat dopamine transporters expressed in LLC-PK$_1$, COS-7 or SKN-M-C cells confirm that the affinity of dopamine for both these transporters is more than two-fold greater than that of noradrenaline.[28,29] There is some dispute over whether or not the V_{max} for dopamine uptake by the noradrenaline transporter is also greater than that for noradrenaline: this factor could determine whether or not dopamine uptake by the noradrenaline transporter actually exceeds that of noradrenaline. Nevertheless, it seems that the noradrenaline transporter, at least, is not at all substrate selective.

In view of the lack of substrate selectivity of the catecholamine transporters, the specificity of monoamine uptake inhibitors might provide an alternative, and possibly more reliable, criterion for the classification of different transporters. In line with their potent uptake blocking activity, SSRIs have a high (nanomolar) affinity for the cloned 5-HT transporter which is certainly higher than their (micromolar) affinity for catecholamine transporters (Table 10.2). The K_is for displacement of [^{3}H]ligands bound to different cloned transporters have been estimated for a wide range of monoamine reuptake inhibitors and their ranking shows excellent agreement with those derived from measurement of synaptosomal [^{3}H]monoamine uptake. However, of 37 compounds tested for displacement of the selective dopamine transporter ligand, [^{3}H]2-β-carbomethoxy-3- β-(4-fluorophenyl)-tropane (WIN 35428), the lowest K_d (25 nM) was obtained with the SSRI, sertraline.[31] In fact, the affinity of this SSRI is two-fold higher than that of nomifensin, a compound regarded

Table 10.2. Binding of SSRIs to cloned human monoamine transporters

	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Zimelidine
5-HT transporter[a]	1.2	0.8	2.2	0.1	0.3	152
Noradrenaline transporter[a]	4K[a]/>1K[b]	240	1.3K	40[a]/312[b]	420	9.4K
Dopamine transporter[a]	28K	4K	9.2K	490	25	12K[a]/ 6K[b]

Values show [a]K_ds or [b]K_is (nM). From data cited in refs 27,30,31.

as a potent dopamine reuptake inhibitor. Findings such as these undermine the possibility that it is the inhibition of 5-HT reuptake by the 5-HT transporter which accounts for the antidepressant actions of SSRIs.

Another point to emerge from these displacement studies is that, even within individual reports, the absolute values for the estimated K_is depend on the choice of radioligand. Almost without exception, displacement of [^{3}H]labeled uptake inhibitors yield lower K_is than those obtained with a [^{3}H]labeled monoamine (e.g., ref. 32). The most likely explanation for this disparity is that different types of ligand bind to different sites on the transporter protein.[33-35] As a result of this, a reduction in binding of a given radioligand is not necessarily due to its competitive displacement. Furthermore, different uptake inhibitors seem to modify transporter function in different ways.[23] For instance, some compounds, notably sertraline, reduce the rate at which the radioligand dissociates from the noradrenaline transporter suggesting that they 'stabilize' the binding of substrates to the transporter.[36]

Contrasting with these detailed studies, the effects of SSRIs on the uptake of [^{3}H]monoamines by different types of cloned catecholamine transporters have not been investigated systematically. The K_is for inhibition of [^{3}H]noradrenaline uptake by paroxetine (312 nM) and citalopram (1 μM), but not that of other SSRIs, by cloned noradrenaline transporters have been reported (see ref. 18) and these are reasonably close to those for inhibition of [^{3}H]monoamine uptake by synaptosomes. However, the K_is of SSRIs for inhibition of [^{3}H]dopamine uptake by the cloned dopamine transporter do not seem to have been reported for any of the SSRIs.

A further complication is that there are two mRNAs for noradrenaline transporters, both of which hybridize to the human noradrenaline transporter cDNA probe.[27] This could mean that there is more than one transcription product of the gene (or two distinct but homologous genes) for the noradrenaline transporter, a possibility which is supported by evidence that these two mRNAs have different distributions in the brain. The larger species (5.8 kb) is prominent in the brainstem and adrenal gland while the smaller (3.6 kb) is thought to represent a glial transporter. Pharmacologically distinct modes of uptake (neuronal uptake, 'uptake$_1$' and extraneuronal uptake, 'uptake$_2$') have been recognized in the periphery for over 30 years but there is now evidence for the existence of several functionally distinct noradrenaline uptake sites. These have been found in rat liver,[37] cultured human glia cells[38]

and cultured brain astrocytes.[39] The underlying explanation for these different uptake processes is as yet unresolved but these findings could point the way to transporters which differ in their sensitivity to different types of monoamine reuptake inhibitors. Even if there turn out to be no overt differences in composition of these transporters, functional differences could arise from post-translational glycosylation or phosphorylation of a single gene product.[19] Further evidence for functionally distinct noradrenaline uptake sites is discussed below.

Substrate Selectivity and Inhibitor Sensitivity of Native Transporters

Studies of [^{3}H]monoamine uptake by intact tissues in vitro or in vivo generally support the view that the 5-HT transporter is substrate selective. For instance, a high concentration of noradrenaline (10 μM) has no effect on uptake of [^{3}H]5-HT in the lung suggesting that there is normally no uptake of the former monoamine by the 5-HT transporter.[40] However, the selectivity of catecholamine transporters in the brain was questioned some time ago in the light of tentative evidence that substantial amounts of noradrenaline are taken up by dopaminergic neurons.[41] Moreover, high concentrations of 5-HT (50μM) reduce net uptake of [^{3}H]noradrenaline in the lung.[40] If this finding generalizes to the brain, accumulation of extraneuronal 5-HT following treatment with an SSRI could well reduce noradrenaline clearance. However, the following section argues that even direct effects of SSRIs on monoamine uptake cannot be ruled out.

The Selectivity of SSRIs as Inhibitors of 5-HT Uptake

Evidence that SSRIs selectively inhibit neuronal uptake of 5-HT derives from several different types of experiments carried out both in vitro and ex vivo, some of which have been mentioned already. The most comprehensive approach has been to measure inhibition of [^{3}H]monoamine uptake into synaptosomes prepared from various regions of the rodent brain.

Several points arise from such experiments. The first, and possibly the most important point, is that in all but one of the published synaptosomal studies, inhibition of uptake of different [^{3}H]monoamines was compared across different brain regions. Yet, it cannot be assumed that uptake of any of the monoamines is the same throughout the brain. On the contrary, as early as 1975, Wong et al[42] pointed out that inhibition of [^{3}H]5-HT uptake by fluoxetine ranged from 2-70%, being greatest in the cortex, intermediate in the striatum and insignificant in the cerebellum. Similar arguments apply to [^{3}H]dopamine uptake: fluoxetine inhibits uptake of this monoamine at nanomolar concentrations in the hippocampus and frontal cortex but has negligible effects in the striatum.[43-44] This is almost certainly a function of the different densities of each type of transporter in different brain regions and/or the rate of spontaneous release of monoamines.

Secondly, it is the IC_{50} for inhibition of [^{3}H]monoamine uptake which is often quoted when comparing the effects of different compounds (even across different studies). However, as emphasized by Bolden-Watson and Richelson,[45] IC_{50}s are influenced by many key experimental variables such as the concentration of competing [^{3}H]monoamine, pH and Na^+ concentration in the incubation medium. K_is should not be affected by these variables but, even so, estimates vary considerably from study to study (see also ref.46) (Table 10.3).

There is only one published report in which synaptosomes derived from the same tissue (the hypothalamus) were used to compare K_is for inhibition by SSRIs of uptake of different [^{3}H]monoamines.[51] Although this has made little difference to their rank order of selectivity (Table 10.4), the absolute selectivity ratio for fluoxetine (20-fold in favor of 5-HT versus noradrenaline) was less than half the 55-fold estimate which is widely quoted. In fact in one study, using slices of rat cortex, the selectivity for inhibition of 5-HT versus noradrenaline

uptake was only 2-fold.[53] This means that fluoxetine could be even less selective in vivo than clomipramine, a compound which is widely regarded as a preferential inhibitor of 5-HT uptake, but is never described as an SSRI.

Given that even the most conservative estimate of the K_i for inhibition of noradrenaline uptake by fluoxetine is about 10 μM, and that of its active metabolite, norfluoxetine, is even less (0.1 μM), it is worth considering whether noradrenaline reuptake might be inhibited at clinical doses of this drug. After chronic administration of a therapeutic dose in humans, plasma levels of fluoxetine and norfluoxetine are between 0.5-1.5 μM[54,55] and their concentration in the brain is probably even higher.[56,57] Even assuming a free fraction of only 5% (see Chapter 2) then, since estimates of the K_i for inhibition of [^{3}H]noradrenaline uptake by this SSRI lie between 0.1-10 μM (Table 10.3), fluoxetine could cause some inhibition of noradrenaline reuptake in the clinical context. Similarly, the plasma concentration of citalopram (285 nM) after chronic administration of the recommended therapeutic dose (40 mg daily) is about 100 times greater than its K_i for inhibition of 5-HT uptake (1-10 nM) and its corresponding brain concentration is 10-fold greater still.[58] This means that, in the therapeutic context, the concentration of citalopram (the most selective SSRI) is close to its K_i for inhibition of noradrenaline reuptake (4 μM).

A further intriguing finding emerged in the course of investigating whether or not there was a target for inhibition of noradrenaline reuptake by SSRIs on noradrenergic neurons. Whereas, in microdialysis studies, the increase in extracellular noradrenaline concentration caused by intracortical infusion of fluoxetine was abolished by a selective chemical lesion of noradrenergic neurons (induced by the neurotoxin, DSP-4), the lesion did not reduce the inhibition of [^{3}H]noradrenaline uptake by the same concentrations of fluoxetine in cortical synaptosomes.[14] This suggests that there could be a target for inhibition of noradrenaline uptake by fluoxetine which is not on noradrenergic neurons. However, in parallel experiments, the DSP-4 lesion affected neither the increase in noradrenaline efflux nor the inhibition of synaptosomal [^{3}H]noradrenaline uptake caused by citalopram.[14] These findings cannot be explained by differences in the affinity of these SSRIs for transmitter receptors which might modulate noradrenaline release. In fact, the only explanation consistent with all the findings from this study is that there are at least two functionally distinct transporters for noradrenaline which differ in their sensitivity to fluoxetine and citalopram. It remains to be seen whether these different uptake sites are the products of the different mRNAs detailed above or whether it is their location in relation to the noradrenaline release sites which is the distinguishing factor (see ref. 14).

Modulation of Catecholamine Release by SSRIs

Direct Receptor Interactions

An increase in extracellular catecholamine concentration could indicate that SSRIs directly activate somatodendritic receptors which increase the firing rate of these neurons and that this leads to an increase in transmitter release. However, SSRIs seem to have either no consistent effects on,[59] or reduce,[60-62] the firing rate of noradrenergic neurons in the brain. So far, their effects on the firing rate of dopaminergic neurons do not seem to have been reported.

Alternatively, SSRIs could bind to receptors for other neurotransmitters which modify monoamine release (heteroceptors). A great deal of attention has been devoted to the binding of SSRIs to H_1, muscarinic and α_1-adrenoceptors. This is understandable because a major objective in their development was to avoid the orthostatic hypotension, cardiotoxicity and sedation which were only too evident with the tricyclic antidepressants and which are a direct result of, or aggravated by, antagonism of these receptors. Binding of SSRIs to other

Table 10.3. K_is for inhibition of [^{3}H]monoamine uptake by SSRIs

		Ki (nM)					
Brain Region	**Reference**	**Citalopram**	**Fluoxetine**	**Fluvoxamine**	**Paroxetine**	**Sertraline**	**Zimelidine**
5-HT (nM)		1.3-10	11-269	4-7	0.5-25	3-13	57-150
Whole brain	42,47						
Cerebral cortex	42,45,48						
Frontal cortex	49						
Hypothalamus	51						
Human placenta	52						
Dopamine (nM)		28000	1600-15000	5000	1100-1700	260	4400
Whole brain	42,47						
Striatum (nM)	42,44,49,51						
Noradrenaline (nM)		3900-4000	143-10000	500-1100	33-350	220	3200-8600
Whole brain	42,47						
Occipital cortex	49						
Hippocampus	45						
Hypothalamus	51						

Unless otherwise stated, all estimates are derived from rat tissues.

Table 10.4. Relative selectivity of SSRIs when uptake of [^{3}H]5-HT and [^{3}H]noradrenaline are measured in synaptosomes derived from the same tissue (hypothalamus)

Fluoxetine	20
Zimelidine	50
Fluvoxamine	177
Paroxetine	318
Citalopram	1500

Data from ref. 51
(N.B. the selectivity for inhibition of 5-HT versus noradrenaline increases with the size of the ratio)

transmitter receptors, particularly those for monoamines, has attracted less attention but details of their affinities for a range of monoamine and other neurotransmitter receptors are given in Table 10.5. It is clear that, when compared with the other SSRIs, fluoxetine binds appreciably to 5-HT$_{2A/2C}$ receptors while sertraline has a relatively high affinity for α1 and α_2-adrenoceptors (Table 10.6). Although binding studies alone give no clues to receptor efficacy (i.e., whether binding reflects agonist or antagonist interactions), recent reports suggest that fluoxetine is a silent antagonist at the former receptor subtype.[64] Another notable finding is that all the SSRIs, as do other antidepressants, have a high affinity for σ_1-receptors.[66] There is growing interest in the possibility that modulation of NMDA- and 5-HT$_{2A}$ receptor[66] function by σ-receptor ligands could well be relevant to the therapeutic effects of all antidepressants. Whether or not this turns out to be the case, binding of SSRIs to any of these receptors could influence catecholamine release either directly or indirectly. One prominent possibility is that SSRIs augment catecholamine release by increasing the extracellular concentration of 5-HT. This could lead to indirect activation of 5-HT receptors on catecholaminergic nerve terminals (heteroceptors) and/or axosomatic or axodendritic receptors in the brainstem nuclei thereby modifying terminal release of transmitter and neuronal activity, respectively. To the extent that there are any consistent findings, these are summarized in Table 10.7.

Effects in the Noradrenergic Terminal Field

It has been acknowledged for many years that 5-HT alters release of catecholamines from peripheral neurons, particularly those in the cardiovascular and enteric systems. Although it is now apparent that extracellular 5-HT could have similar effects on catecholaminergic transmission in the brain, details of the type and location of the receptors which mediate these changes are far from clear.

5-HT$_1$ and 5-HT$_2$ Receptors

Judging by the little evidence gathered to date, 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors in the terminal field seem to have no influence on noradrenaline release.[67,68] However, the 5-HT$_{2A/2C}$ agonist, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) increases noradrenaline release in the hypothalamus[69] and hippocampus.[67] Further evidence for a role for these receptors in modulation of noradrenaline release comes from studies showing that

2-methyl-5-HT, blunts glutamate-evoked release of noradrenaline in hypothalamic slices.[70] Although this compound is a 5-HT_3 receptor agonist, the increase in efflux was prevented by α-methyl-5-HT, a 5-$HT_{2A/2C}$ receptor agonist. In contrast, 5-HT-mediated inhibition of noradrenaline release is augmented by coperfusion with methysergide, a non-selective 5-$HT_{1/2}$ receptor antagonist.[70] Both these findings are consistent with the possibility that activation of 5-HT_2 receptors in the terminal field increases noradrenaline release. The location of these receptors, i.e., whether they are true heteroceptors or whether they form part of a local polysynaptic loop, is as yet unknown.

5-HT_3 Receptors

One of the first suggestions that 5-HT modulates release of noradrenaline in areas of the brain innervated by noradrenergic nerve terminals came from studies of rabbit hippocampal slices. Electrically-evoked release of [^{3}H]noradrenaline from preloaded slices was increased by 5-HT or the 5-HT_3 receptor agonist, 2-methyl-5-HT; this increase was prevented by the 5-HT_3 receptor antagonists: 3-tropanyl-3,5-dichlorobenzoate (MDL 72222) or ICS 205-930 ('tropisetron'),[71] albeit at moderately high concentrations. Essentially similar results were obtained in analogous studies of the rat hippocampus and hypothalamus.[67]

Although it is evident that activation of 5-HT_3 receptors augments noradrenaline release in these tissues, the question remains at to whether it is a population of 5-HT_3 heteroceptors which is responsible for this increase. Certainly, the hippocampus is richly endowed with 5-HT_3 receptors but is not at all certain that there are any 5-HT_3 receptors on noradrenergic terminals in forebrain areas.[72] It has even been claimed that several 5-HT_3 receptor ligands, including 2-methyl-5-HT and even 5-HT itself, are ligands for α_2-adrenoceptors and this accounts for any changes in noradrenaline release.[73] However, 5-HT_3 receptor agonists can increase electrically-evoked hippocampal noradrenaline release even when there is no apparent activation of terminal α_2-autoreceptors.[67]

To complicate matters yet further, K^+-evoked release of endogenous noradrenaline from rat hypothalamic slices is reduced by 2-methyl-5-HT[69] and, in microdialysis studies, local infusion of 5-HT reduces K^+-evoked noradrenaline release in the hippocampus.[5] In both cases, the response is prevented by co-administration of a 5-HT_3-receptor antagonist. Which of the many methodological differences between these studies and those described above explains their disparate results is unresolved? One possibility is that the mechanisms regulating release of endogenous noradrenaline stores are not the same as those for stores loaded with exogenous [^{3}H]transmitter. Another is that electrical and K^+-evoked stimulation mobilize different pools of releasable transmitter

Modulation of noradrenaline release by 5-HT_3 receptors has considerable bearing on the actions of SSRIs. Echoing the findings described above, paroxetine increases electrically-evoked release of [^{3}H]noradrenaline from preloaded hippocampal slices[67] while fluoxetine reduces K^+-evoked release from endogenous noradrenaline stores in this brain region.[5] Both these changes are prevented by 5-HT_3 receptor antagonists suggesting that they are mediated by 5-HT as it accumulates in the synaptic cleft. Thus, although 5-HT-induced changes in noradrenaline release, mediated by 5-HT_3 receptors, could occur when SSRIs are used in the clinical context, it is currently unclear whether this accounts for the increase in the extracellular concentration of noradrenaline seen after their systemic administration.

5-HT_4 Receptors

Unlike the dopaminergic system (see below) there have been no systematic studies of the effects of 5-HT_4 receptor ligands on noradrenaline release in the brain.

Table 10.5. Receptor binding of SSRIs

Receptor	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Zimelidine
α_1[a]	1.9K	3.8-5.9K	7.5K	4.6K	380	1.5K
α_2[a]	15.3K	13-14K	15K	17K	4.1K	790
β[b] (rat)	>5K	>5K	>5K	>5K		>5K
5-HT_{1A}[b] (rat)	190K[b]	150K	200K		436K[b]	
5-HT_{2A}[b] (rat)	25K[b]	280[a]/1.7K[b]	31K	19K[a]	9.9K[a]/24K[b]	
5-HT_{2C}[b] (pig)	26K[b]	1.5K	890K		11K	
D_2[a]		12K		32K	10.7K	
Muscarinic[a]	2.2K	590-2K	24K	108	630	13K
H_1[a]	470	5.4-6.2K	109K	22K	24K	4K
σ_1[b] (rat)	292	240	36	1.9K	57	
σ_2[b] (rat)	5.4K	16.1K	8.4K	23K	5.3.K	

Values derived from human tissue, unless otherwise stated, and represent either [a]K_ds or [b]K_is. From data cited in refs. 51,63-65.

Table 10.6. Rank order of affinity for receptor binding

Receptor	K_d or K_i (nM)		
	<1 μM	**1-10 μM**	**> 10 μM**
α_1	sert>	zimel>cital>fluox≥parox>fluvox	
α_2	zimel>	sert>	fluox>fluvox≥cital>parox
5-HT_{1A} (rat)			fluox>cital>fluvox>sert
5-HT_{2A} (rat)		fluox>	sert≥cital>fluvox
5-HT_{2C} (pig)		fluox>	sert>cital>>fluvox
DA_2			sert>fluox>parox
Muscarinic	parox>sert	fluox>cital>	zimrl>fluvox
H_1	cital>	zimel>fluox>	parox≥sert>>fluvox
σ_1	fluvox>sert>fluox>cital	parox	
σ_2		sert=cital>fluvox>	fluox>parox

cital,citalopram; fluox, fluoxetine; fluvox, fluvoxamine; parox, paroxetine; sert, sertraline.
Sequences derived from 'within study' K_ds orK_is

Table 10.7. Effects of 5-HT receptor activation on catecholamine release

	Noradrenergic		Dopaminergic	
	terminal field	**polysynaptic**	**terminal field**	**polysynaptic**
5-HT_{1A}	no effect	↑ (especially in anesthetized subjects)	no effect	↑
5-HT_{1B}	no effect		↑	
5-$HT_{2A/2C}$	↑	↓(especially in awake subjects)	?	
5-HT_3	↑(electrical stimulation of [3H] preloaded stores		↑?	
	↓(K^+-evoked release from endogenous stores)			
5-HT_4			↑	

Arrows indicate an increase (↑), a reduction (↓), or no effect on, catecholamine release caused by activation of 5-HT receptors in catecholaminergic projection areas, or at some point in a polysynaptic loop (most likely incorporating monoamine brainstem nuclei).

Effects Incorporating Noradrenergic Brainstem Nuclei

It is difficult to unravel the type and location of 5-HT receptors involved in modulation of noradrenaline release after systemic administration of test compounds not least because receptors anywhere in the brain or periphery, i.e., not only those in the terminal field, will be recruited. However, when considering the effects of 5-HT on release of noradrenaline, the brainstem nuclei will be prominent targets for drugs which modulate noradrenaline release.

Important interactions between serotonergic and noradrenergic systems in the brainstem are suggested by the dense serotonergic innervation of the locus coeruleus, the complex of nuclei (largely comprising the A_6, locus coeruleus proper) which is the source of the majority of noradrenergic terminals in forebrain areas. The origin of these serotonergic neurons is uncertain but the median and B_9 raphé nuclei as well as the pericoerulear halo region are thought to be important sources.[74] There is more controversy over whether or not there is a contribution from the dorsal raphé nucleus.[75,76]

Many findings suggest that serotonergic afferents inhibit neuronal activity in the locus coeruleus. For instance, a serotonergic lesion increases both tyrosine hydroxylase activity,[77] the rate-limiting enzyme in noradrenaline biosynthesis, and the firing frequency [78]of neurons in this nucleus. Yet, inhibition of 5-HT synthesis with *p*-chlorophenylalanine (*p*CPA) has inconsistent effects: an increase[79,80] and no change[81] in the spontaneous firing rate of locus neurons have been reported. 5-HT also seems to blunt the noradrenergic response to sensory stimuli. In particular, iontophoretic administration of 5-HT in the locus coeruleus attenuates the increased firing caused by local infusion of glutamate, the excitatory amino acid neurotransmitter which is released in response to excitation of sensory afferents.[82] The following sections discuss the receptors which might be involved in such processes.

5-HT$_1$ Receptors

The effects of 5-HT$_{1A}$ receptor agonists on the firing frequency of noradrenergic neurons in the locus coeruleus are not at all clear (c.f., refs. 78,83-85) possibly because of the confounding factor of anesthesia and the questionable selectivity of test agents. A recent study has avoided this problem by using c-*fos* expression as a marker for neuronal activity in conscious rats. This was increased markedly in the locus coeruleus after systemic administration of the selective 5-HT$_{1A}$ receptor agonists, ipsapirone and tandispirone. Moreover, the increase was prevented by the selective 5-HT$_{1A}$ antagonist, N-tert-butyl-3[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropionamide (WAY-100135).[86]

In line with a 5-HT$_{1A}$ receptor-induced excitation of noradrenergic neurons in the locus coeruleus, microdialysis studies have shown a large increase in efflux of noradrenaline in the hippocampus[87,88] or cortex[89] of conscious rats after systemic administration of the selective 5-HT$_{1A}$ receptor agonists, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) or buspirone, respectively. However, the animals' state of arousal turns out to be a key variable because 8-OH-DPAT had no such effect in anesthetized subjects.[87] This is mirrored by the finding that the 5-HT$_{1A}$ receptor antagonist, ((N(-)[2(-)[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride (WAY 100635) has no effect on noradrenaline efflux in awake rats[90] but reduces the firing rate of noradrenergic neurons in anesthetized subjects.[78] All these findings suggest that there is more tonic activation of 5-HT$_{1A}$ receptors in anesthetized than awake rats.

As regards the question of where the 5-HT$_{1A}$ receptors are located, it is unlikely that they are in the noradrenergic terminal field because systemic administration of the selective 5-HT$_{1A}$ agonist, 5-{3-[[(2S)-1,4-benzodioxan-2-ylmethyl]amino]propyl}-1,3-benzodioxole hydrochloride (MCK 242), increased efflux of noradrenaline in the hypothalamus whereas local infusion of 8-OH-DPAT did not.[68] The 5-HT$_{1A}$ receptors do not seem to be on serotonergic neurons either because neither a 5,7,-dihydroxytryptamine lesion nor *p*CPA prevents the increase in noradrenaline efflux caused by systemic administration of a 5-HT$_{1A}$ receptor agonist.[10,68,88] Finally, WAY 100635 has no effect on noradrenergic firing frequency when infused into the locus coeruleus but reduces it when given systemically.[78] All this evidence suggests that activation of 5-HT$_{1A}$ receptors increases noradrenaline release but that these receptors are located neither in the locus coeruleus nor on serotonergic neurons. Clearly, this point merits further investigation.

Finally, recent findings indicate that, although a serotonergic lesion increases the firing frequency of noradrenergic neurons in the locus coeruleus of anesthetized rats, it abolishes the reduction in firing frequency seen in unlesioned rats after systemic injection of a 5-HT$_{1A}$ antagonist.[78] These findings can be explained only if noradrenergic neurons are subject to dual control, with 5-HT$_{1A}$ receptors increasing their activity and a different 5-HT receptor blunting it: 5-HT$_2$ receptors could be candidates for this role (see page 163).

5-HT$_2$ Receptors

It has been known for some time that either local or systemic infusion of 5-HT$_{2A}$ receptor agonists depresses the spontaneous firing rate of noradrenergic neurons in the locus coeruleus.[91,92] In anesthetized subjects, there seems to be little tonic activation of these receptors because iontophoretic application of 5-HT$_2$ receptor antagonists into the locus coeruleus does not affect neuronal firing rate.[84] These receptors are probably not on serotonergic neurons because the depression of firing is little affected by either a 5,7-dihydroxytryptamine lesion or *p*CPA. They could modulate the activity of afferent neurons releasing amino acid neurotransmitters in the locus coeruleus.[93] Whether their activation results in excitation or inhibition of locus firing could depend on whether the tonic activity of GABAergic or glutamatergic neurons is the most prominent. This would be consistent with evidence that 5-HT$_{2A}$ receptor agonists depress basal firing rate (increase GABAergic activity?) but augment the response to sensory stimulation of the sciatic nerve[89] (increase glutamatergic activity?).

In line with the inhibition of spontaneous neuronal firing by 5-HT$_2$ agonists, microdialysis studies have shown that systemic administration of the 5-HT$_{2A/2C}$ agonist, DOI, depresses efflux of noradrenaline in the hippocampus of anaesthetized rats, a change which is prevented by systemic administration of the 5-HT$_{2A/2C}$ receptor antagonist, ritanserin.[94] Although ritanserin alone has no consistent effects in anaesthetized rats, it increases noradrenaline efflux in conscious subjects.[87] Unlike, 5-HT$_{1A}$ receptors (see page 162), tonic activation of 5-HT$_{2A}$ receptors seems to be increased in awake rats, therefore. This possibly reflects differences in the tonic activity of amino acid inputs in anesthetized and awake animals.

Effects in the Dopaminergic Field

As with noradrenaline, the effects of 5-HT on dopamine release in vitro depend on the test procedure. For instance, in striatal slices, 5-HT reduces the K±evoked release of transmitter from preloaded [^{3}H]dopamine stores[95,96] but increases spontaneous release of endogenous dopamine.[97] Again, reasons for these disparate results are unresolved but they could indicate that different pools of transmitter are mobilized for release under these different experimental conditions. There is, nonetheless, general agreement that 5-HT can modulate dopamine release; the receptors which could mediate these changes are discussed below.

5-HT$_1$ Receptors

Early slice studies suggested that neither release of endogenous dopamine in the terminal field[97] nor the inhibition of [^{3}H]dopamine release by 5-HT in the striatum[96] is influenced by either 5-HT$_{1A}$ or 5-HT$_{1B}$ receptors. This is borne out to some extent by microdialysis studies in vivo in which local infusion of the selective 5-HT$_{1A}$ receptor agonist, 8-OH-DPAT, had a negligible effect on dopamine efflux.[9] However, both 5-HT itself and activation of 5-HT$_{1B}$ receptors, by local infusion of the selective 5-HT$_{1B}$ agonist, 7-trifluoromethyl-4(4-methyl-l-piperazinyl)-pyrrolo[1,2-a]quinoxaline maleate (CGS 12066B), cause a prominent increase in dopamine efflux in the striatum.[98] Similar results have been found using the 5-HT$_{1B}$ receptor agonist, 3-[1,2,5,6-tetrahydropyrid-4-yl]-pyrrolo-[3,2-b]pyrid-5-one (CP-93,129).[99] Presumably, these would have to be 5-HT$_{1B}$ heteroceptors because activation of presynaptic 5-HT$_{1B}$ receptors on serotonergic nerve terminals depresses release of 5-HT. An alternative explanation is that dopamine is taken up by, and released from, serotonergic neurons and it is this release which is modulated by 5-HT$_{1B}$ autoreceptors (see page 165 and ref. 100).

5-HT$_2$ Receptors

5-HT$_{2A/2C}$ receptor ligands do not seem to affect release of endogenous dopamine from striatal slices[97] but their influence on release from [^{3}H]dopamine-preloaded striatal slices is far from clear. One report suggests that neither a selective 5-HT$_{2A}$ antagonist (ketanserin) nor a non-selective 5-HT$_{2A/2C}$ antagonist (ritanserin) attenuates the 5-HT-induced increase in release of [^{3}H]dopamine in either the striatum or nucleus accumbens.[101] However, another report suggests that K^+-evoked release of [^{3}H]dopamine is blunted by 5-HT acting at 5-HT$_{2A}$ receptors.[96] These disparate results evidently need further investigation.

Results from experiments using microdialysis in vivo broadly favor the notion that dopamine release in the brain can be modulated by 5-HT$_{2A/2C}$ receptors. However, contrasting with in vitro studies, activation of 5-HT$_{2A/2C}$ receptors increases dopamine efflux in the nucleus accumbens.[102] This could well be mediated by 5-HT$_{2C}$ receptors alone because, in the striatum, the effects of 5-HT are not influenced by selective 5-HT$_{2A}$ receptor antagonists (e.g., ketanserin). Moreover, the 5-HT$_{2C}$ agonist, 1-(3-chlorophenyl) piperazine (*m*CPP), increases release in this tissue,[9] although a 5-HT$_{1B}$ receptor involvement in the actions of *m*CPP cannot be ruled out.

Clearly, the marked disparities between results obtained from in vitro and in vivo studies must be reconciled. Meanwhile, it is unclear whether 5-HT$_{2A/2C}$ receptors modulate dopamine release in the terminal field and, if they do, in what way.

5-HT$_3$ Receptors

In striatal slices, 5-HT increases spontaneous and K^+-evoked release of endogenous dopamine; this is mimicked by the 5-HT$_3$ receptor agonist, 2-methyl-5-HT and inhibited by 5-HT$_3$ receptor antagonists.[97] Tetrodotoxin does not abolish the 5-HT-induced increase in efflux, suggesting that at least some of these 5-HT$_3$ receptors could be on dopaminergic nerve terminals.

However, not all studies support this scheme. The 5-HT$_{3/4}$ antagonist, tropisetron, had no effect on 5-HT-induced release of [^{3}H]dopamine from slices of either the striatum or the nucleus accumbens.[101] Similarly, neither of the 5-HT$_3$ receptor antagonists, MDL 72222 or ondansetron, prevented the 5-HT-induced increase in basal and Ca^{2+}-evoked release of [^{3}H]dopamine from synaptosomes prepared from striatal tissue.[103] In view of this finding in synaptosomes then, even if it is assumed that 5-HT$_3$ receptors do modulate dopamine release, they are unlikely to be on dopaminergic nerve terminals. Again, at least some of these disparate findings could reflect differences in the modulation of release of dopamine from endogenous and [^{3}H]dopamine preloaded stores. Particularly relevant to this problem is evidence that exogenous [^{3}H]dopamine accumulates in noradrenergic and serotonergic as well as dopaminergic neurons.[104,105] Consequently, [^{3}H]dopamine released from preloaded stores might not be derived from dopaminergic neurons alone.

Studies in vivo, using microdialysis have not resolved these problems. In the nucleus accumbens,[106] the prefrontal cortex,[107] or the striatum,[108] 5-HT$_3$ receptor antagonists (e.g., ondansetron) prevent the increase in dopamine efflux induced by a 5-HT$_3$ receptor agonist. This is not affected by a selective serotonergic lesion suggesting that these receptors are not on serotonergic nerve terminals.[106] However, neither basal dopamine efflux nor the increase in dopamine efflux caused by raising extracellular Ca^{2+} concentration were affected by infusion of 5-HT$_3$ receptor antagonists.[109] Although few of these studies were carried out on freely-moving subjects, these disparate findings are not obviously explained by any effects of anesthesia.

5-HT_4 Receptors

Inevitably, recent research of 5-HT_3 receptors has revealed that several drugs, originally thought to be selective 5-HT_3 ligands, bind to 5-HT_4 receptors also: tropisetron is a case in point. Furthermore, the increase in striatal dopamine efflux caused by 5-HT is blunted by the 5-$HT_{3/4}$ receptor antagonist, endo-6-methoxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl-2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxylate hydrochloride (DAU 6285) and mimicked by a novel, 5-HT_4 receptor agonist, endo-N-(8-methyl-8-azabicyclo-[3.2.1.]oct-3-yl)-2,3-dihydro-(1-methyl)ethyl-2-oxo- 1H-benzimidazole-1-carboxamide hydrochloride (BIMU 8).[110] There is some evidence that BIMU 8 is also a σ_2-receptor antagonist, but it is as yet not known how this might affect dopamine efflux. However, changes in dopamine efflux have been confirmed using several combinations of different 5-HT_4 receptor agonists and antagonists,[110] making these receptors the most likely functional target. As Bonhomme et al point out,[109] modulation of dopamine release by 5-HT_4 receptors is entirely consistent with their high density in the striatum when compared with that of 5-HT_3 receptors.

Dopamine Transporters

The dopamine transporter could also have a role in the modulation of dopamine release by 5-HT. This was first suggested by the finding that selective dopamine uptake blockers, or high (i.e., non-selective) concentrations of fluoxetine (>1 μM), block [^{3}H]dopamine release evoked by 5-HT (up to 100 μM) from slices of the nucleus accumbens or striatum.[101,111] It has been known for some time that the 5-HT-evoked release of [^{3}H]dopamine from striatal synaptosomes is additive with that caused by a depolarizing pulse of K^+.[112] More recently, it has been reported that, in a microdialysis study, the 5-HT-induced increase in striatal dopamine efflux is prevented by the dopamine uptake inhibitor, nomifensin.[113] To add to this problem, certain 5-HT receptor ligands are thought to modify the function of the dopamine transporter. For instance, the 5-HT_3 receptor agonist, phenylbiguanide, increases the release of [^{3}H]dopamine from striatal synaptosomes and this effect is blocked by nomifensin rather than 5-HT_3 receptor antagonists.[114]

All these findings suggest that some compounds which are regarded as 5-HT_3 receptor ligands, including 5-HT itself (especially at high concentrations), could well release dopamine by promoting its export by a membrane transporter. It should be borne in mind that, at clinical doses, SSRIs are unlikely to bind appreciably to the dopamine transporter (see section: SSRIs and extracellular catecholamines). This means that, by increasing the concentration of extracellular 5-HT, SSRIs could increase transporter-dependent release of dopamine in the terminal field.

Effects Incorporating Dopaminergic Brainstem Nuclei

Serotonergic neurons in the raphé nuclei innervate dopaminergic nuclei in the substantia nigra (A_9) and the lateral tegmentum (A_{10}). They also directly innervate dopaminergic projection areas such as the striatum and nucleus accumbens. There is therefore plenty of scope for 5-HT to modulate dopaminergic transmission in the brain through activation of receptors in the terminal field and/or somatodendritic receptors in dopaminergic nuclei.

In general, serotonergic neurons inhibit the firing rate of dopaminergic neurons (e.g., ref. 115). Evidence that systemic administration of 8-OH-DPAT, at concentrations specific for presynaptic 5-HT_{1A} receptors, increases dopamine efflux in the ventral tegmental area[10] is consistent with this view. This increase, which is abolished by pretreatment with *p*CPA could be explained by activation of 5-HT_{1A} autoreceptors in the raphé nuclei which will depress the firing rate of inhibitory serotonergic afferents to the ventral tegmental area.

However, infusion of 5-HT or the 5-HT_{1A} receptor agonist, 8-OH-DPAT, into the dorsal raphé nucleus reduces dopamine efflux in the nucleus accumbens[116] and striatum.[9] Also, stimulation of the dorsal raphé nucleus, by infusion of glutamate, increases efflux of dopamine in the nucleus accumbens.[116] These changes could possibly reflect direct effects of serotonergic neurons innervating the terminal projection areas of dopaminergic neurons, i.e., they are not dependent on the activity of inhibitory serotonergic afferents in the ventral tegmental area.

Another problem making interpretation of these findings far from straightforward is evidence that 5-HT increases the reverse efflux of dopamine by a membrane transporter. Thus, in slices of the ventromedulla (i.e., incorporating the A_9 and A_{10} dopaminergic nuclei), 5-HT increased spontaneous release of [^{3}H]dopamine; this increase was unaffected by any of a wide range of 5-HT receptor ligands but it was prevented by pre-incubation of the slices with fluoxetine.[100] There is also evidence that serotonergic terminals in the ventral tegmental area take up dopamine and that its subsequent release is modulated by 5-HT autoreceptors. Since this latter uptake process is inhibited by fluoxetine, this could mean that SSRIs switch the regulation of dopamine release from a process involving both 5-HT and dopamine autoreceptors to one which is governed by dopamine autoreceptors, only.

It is obviously going to be extremely difficult to establish the effects of SSRIs on interactions between serotonergic and dopaminergic neurons. This is chiefly because any net effects of SSRIs on dopamine release will depend on the net effects on dopamine sequestration by the membrane transporter in vivo and on reverse transport of this transmitter. In turn, these changes could well depend on the subject's state of arousal.

Chronic Treatments

In the past, a great deal of effort has been devoted to investigating the effects of chronic administration of antidepressants on putative neurochemical markers for depression. For many years, the down-regulation of β_1-adrenoceptors was flagged as a common target but this was undermined when it became evident that SSRIs neither downregulate the β-adrenoceptors nor desensitize their second messenger system.

So far, no consistent changes have been reported for either catecholamine receptors,[58,117] catecholamine transporters or their mRNAs after chronic administration of SSRIs[19] but investigations continue on this point. In view of the widely differing chemical structures of the SSRIs, as well as their different profiles for interactions with neurotransmitter receptors, the discovery of any common neurochemical adaptive response to their chronic administration must be regarded as a promising clue to the mechanisms underlying their psychotropic effects.

Conclusion

Investigations of 5-HT-induced changes in catecholaminergic transmission merit caution for a variety of reasons. First, it is possible that the selectivity of monoamine transporters in vivo has been overestimated. Secondly, there is overwhelming evidence, particularly for noradrenaline, that SSRIs could affect catecholaminergic transmission indirectly by increasing the concentration of extracellular 5-HT. Thirdly, recent evidence suggests that SSRIs could influence extrusion of dopamine by a membrane transporter. It is worth noting that a similar process could well exist for noradrenaline,[118] but this does not seem to have been researched in detail.

In short, it is no longer tenable to explain the antidepressant effects of SSRIs in terms of their effects on serotonergic transmission alone. There is clearly scope for more research into the modulation of interactions between serotonergic and catecholaminergic

transmission by antidepressants and how this might influence behavior. This topic is discussed in detail in Chapter 11.

References

1. Hughes ZA, Stanford SC. Increased noradrenaline efflux induced by local infusion of fluoxetine in the rat frontal cortex. Eur J Pharmacol 1996; 317:83-90.
2. Chen N-H, Reith MEA. Effects of locally applied cocaine, lidocaine and various uptake blockers in monoamine transmission in the ventral tegmental area of freely moving rats: A microdialysis study on monoamine interrelationships. J Neurochem 1994; 63:1701-1713.
3. Jordan S, Kramer GL, Zukas PK et al. In vivo biogenic amine efflux in medial prefrontal cortex with imipramine, fluoxetine and fluvoxamine. Synapse 1994; 18:294-297.
4. Perry KW, Fuller RW. Fluoxetine increases norepinephrine release in rat hypothalamus as measured by tissue levels of MHPG-SO_4 and microdialysis in conscious rats. J Neural Transm 1997; 104:953-966.
5. Matsumoto M, Yoshioka M, Togashi H et al. Modulation of norepinephrine release by serotonergic receptors in the rat hippocampus as measured by in vivo microdialysis. J Pharmacol Exp Ther 1995; 272:1044-1051.
6. Gobert A, Rivet J-M, Cistarelli L et al. α_2-Adrenergic receptor blockade markedly potentiates duloxetine- and fluoxetine-induced increases in noradrenaline, dopamine and serotonin levels in the frontal cortex of freely moving rats. J Neurochem 1997; 69:2616-2619.
7. Paez X, Liebowitz S. Changes in extracellular PVN monoamines and macronutrient intake after idazoxan or fluoxetine injection. Pharmacol Biochem Behav 1993; 46: 933-941.
8. Hajós-Korcsok É, Sharp T. Personal communication. 1998.
9. Benloucif S, Galloway MP. Facilitation of dopamine release in vivo by serotonin agonists: Studies with microdialysis. Eur J Pharmacol 1991; 200:1-8.
10. Chen N-H, Reith MEA. Monoamine interactions measured by microdialysis in the ventral tegmental area of rats treated systemically with (±)-8-hydroxy-2-(di-*n*-propylamino)tetralin. J Neurochem 1995; 64:1585-1597.
11. Perry KW, Fuller RW. Effect of fluoxetine on serotonin and dopamine concentration in microdialysis fluid from rat striatum. Life Sci 1992; 50:1683-1690.
12. Li X-M, Perry KW, Fuller RW. On the in vivo modulation of neostriatal dopamine release by fluoxetine and 5-hydroxy-L-tryptophan in conscious rats. J Pharm Pharmacol 1996; 48:825-828.
13. Ichikawa J, Meltzer HY. Effect of antidepressants on striatal and accumbens extracellular dopamine levels. Eur J Pharmacol 1995; 281:255-261.
14. Hughes ZA, Stanford SC. Evidence from microdialysis and synaptosomal studies of rat cortex for noradrenaline uptake sites with different sensitivities to SSRIs. Br J Pharmacol 1998; 124:1141-1148.
15. Sammet S, Graefe K-H. Kinetic analysis of the interaction between noradrenaline and Na^+ in neuronal uptake: Kinetic evidence for cotransport. Naunyn-Schmiedeberg's Arch Pharmacol 1979; 309:99-107.
16. Carlsson l, Abrahamson T. Characterization of the inhibitory effect of some antidepressant drugs on the outward transport of norepinephrine in the ischemic myocardium. J Pharmacol Exp Ther 1988; 247:715-720.
17. Langeloh A, Bönisch H, Trendelenburg U. The mechanism of the ^{3}H-noradrenaline releasing effect of various substrates of uptake$_1$: A multifactorial induction of outward transport. Naunyn-Schmiedeberg's Arch Pharmacol 1987; 336:602-610.
18. Povlock SL, Amara SG. The structure and function of norepinephrine, dopamine and serotonin transporters. In: Neurotransmitter Transporters, Structure, Function and Regulation. Reith MEA, ed. Totowa, New Jersey; Humana Press Inc., 1997:1-28.
19. Blakely RD, Ramamoorthy S, Qian Y et al. Regulation of antidepressant-sensitive serotonin receptors. In: Reith, MEA. ed. Neurotransmitter Transporters: Structure, Function and Regulation. Totowa, New Jersey: Humana Press Inc., 1997:29-72.

20. Rudnick G. Mechanisms of biogenic amine neurotransmitter transporters. In: Reith MEA, ed. Neurotransitter Transporters: Structure, Function and Regulation. Totowa, New Jersey: Humana Press Inc., 1997:73-100.
21. Ramamoorthy S, Bauman AL, Moore KR et al. Antidepressants- and cocaine-sensitive human serotonin receptor transporter: Molecular cloning, expression and chromosomal localization, Proc Natl Acad Sci USA 1993; 90:2542-2546.
22. Austin MC, Bradley CC, Mann JJ et al. Expression of serotonin transporter messenger RNA in the human brain. J Neurochem 1994; 62:2362-2367.
23. Barker El, Blakely RD. Identification of a single amino acid, phenylalanine 586, that is responsible for high affinity interactions of tricyclic antidepressants with the human serotonin transporter. Molec Pharmacol 1996; 50:957-965.
24. Sur C, Betz H, Schloss P. A single serine residue controls the cation dependence of substrate transport by the rat serotonin transporter. Proc Natl Acad Sci USA 1997; 94:7639-7644.
25. Rosenthal NE, Nazzanti CM, Barnett RL et al. Role of serotonin transporter promoter repeat length polymorphism (5-HTTLPR) in seasonality and seasonal affective disorder. Mol Psychiatry 1998; 3:175-177.
26. Jayanthi LD, Prasad PD, Ramamoorthy S et al. Sodium and chloride-dependent cocaine-sensitive, high-affinity binding of nisoxetine to the human placental norepinephrine transporter. Biochemistry 1993; 32:12178-12185.
27. Pacholczyk T, Blakely RD, Amara SG. Expression cloning of a cocaine- and antidepressant-sensitive human noradrenaline transporter. Nature 1991; 350:350-353.
28. Gu H, Wall SC, Rudnick G. Stable expression of biogenic amine transporters reveals differences in inhibitor sensitivity, kinetics and ion dependence. J Biol Chem 1994; 269; 7124-7130.
29. Pifl C, Hornykiewicz O, Giros B et al. Catecholamine transporters and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxicity: studies comparing the cloned human noradrenaline and human dopamine transporter. J Pharmacol Exp Ther 1996; 277:1437-1443.
30. Giros, B, Mestikawt S, Godinot N et al. Cloning, pharmacological characterization, and chromosome assignment of the human dopamine transporter. Molec Pharmacol 1992; 42:383-390.
31. Tatsumi M, Groshan K, Blakely RD et al. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. Eur J Pharmacol 1997; 340:249-258.
32. Owens MJ, Morgan WN, Plott SJ et al. Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. J Pharmacol Exp Ther 1997; 283:1305-1322.
33. Pristupa ZB, Wilson JM, Hoffman BJ et al. Pharmacological heterogeneity of the cloned and native human dopamine transporter: Disassociation of [^{3}H]WIN 35,428 and [^{3}H]GBR 12,935 binding. Molec Pharmacol 1994; 45:125-135.
34. Buck KJ, Amara SG. Structural domains of catecholamine transporter chimeras involved in selective inhibition by antidepressants and psychomotor stimulants. Molec Pharmacol 1995; 46:1030-1037.
35. Erreboe I, Plenge P, Mellerup ET. Differences in brain 5-HT transporter dissociation rates among animal species. Pharmacol Toxicol 1995; 76:376-379.
36. Plenge P, Mellerup ET An affinity-modulating site on neuronal monoamine transport proteins. Pharmacol Toxicol 1997; 80:197-201.
37. Martel F, Azevedo I, Osswald W. Uptake of ^{3}H-catecholamines by rat liver cells occurs mainly through a system which is distinct from uptake$_1$ or uptake$_2$. Naunyn-Schmiedeberg's Arch Pharmacol 1994; 350:130-142.
38. Russ H, Staudt K, Martel F et al. The extraneuronal transporter for monoamine transmitters exists in cells derived from human central nervous system glia. Eur J Neurosci 1996; 8:1256-1264.
39. Paterson IA, Hertz L. Sodium-independent transport of noradrenaline in mouse and rat astrocytes in primary culture. J Neurosci Res 1989; 23:71-77.
40. Paczkowski NJ, Vuocolo HE, Bryan-Lluka LJ. Conclusive evidence for distinct transporters for 5-hydroxytryptamine and noradrenaline in pulmonary endothelial cells of the rat. Naunyn-Schmiedeberg's Arch Pharmacol 1996; 353:423-430.

41. Michel M, Hiemke C, Ghraf R. Preferential uptake of norepinephrine into dopaminergic terminals of a synaptosomal preparation from rat cerebral cortex. Brain Res 1984; 301:149-152.
42. Wong DT, Bymaster FP, Horng JS et al. A new selective inhibitor for uptake of serotonin into synaptosomes of rat brain: 3-(*p*-trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine. J Pharmacol Exp Ther 1975; 193:804-811.
43. Fleckenstein AE, Beyeler ML, Jackson JC et al. Methamphetamine-induced decrease in tryptophan hydroxylase activity: Role of 5-hydroxytryptaminergic transporters. Eur J Pharmacol 1997; 324:179-186.
44. Chen N-H, Reith MEA. Role of axonal and somatodendritic monoamine transporters in action of uptake blockers. In: Neurotransmitter Transporters, Structure, Function and Regulation. Reith MEA, ed. Totowa, New Jersey; Humana Press Inc., 1997:345-391.
45. Bolden-Watson C, Richelson E. Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes. Life Sci 1993; 52:1023-1029.
46. Stanford SC Prozac: Panacea or puzzle? Trends Pharmacol Sci 1996; 17:150-154.
47. Wong DT, Horng JS, Bymaster FP. A selective inhibitor of serotonin uptake: Lilly 110140, 3-(p-trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine. Life Sci 1974; 15:471-479.
48. Cheng CHK, Costall B, Naylor RJ et al. The effect of 5-HT receptor ligands on the uptake of [^{3}H]5-hydroxytryptamine into rat cortical synaptosomes. Eur J Pharmacol 1993; 239:211-214.
49. Richelson E, Pfenning M. Blockade by antidepressants and related compounds of biogenic amine uptake into rat brain synaptosomes: Most antidepressants selectively block norepinephrine uptake. Eur J Pharmacol 1984; 104:277-286.
50. Cheetham SC, Viggers JA, Slater NA et al. [^{3}H]paroxetine binding in rat frontal cortex strongly correlates with [^{3}H]5-HT uptake: Effect of administration of various antidepressant treatments. Neuropharmacology 1993; 32:737-743.
51. Thomas DR, Nelson DR, Johnson AM. Biochemical effects of the antidepressant paroxetine, a specific 5-hydroxytryptamine uptake inhibitor. Psychopharmacology 1987; 93:193-200.
52. Cool DR, Liebach FH, Ganapathy V. Interaction of fluoxetine with the human placental serotonin transporter. Biochem Pharmacol 1990; 40:2161-2167.
53. Harms HH. The antidepressant agents desipramine, fluoxetine, fluvoxamine and norzimelidine inhibit uptake of [^{3}H]noradrenaline and [^{3}H]5-hydroxytryptamine in slices of human and rat cortical brain tissue. Brain Res 1983; 275:99-104.
54. Baumann P. Pharmacokinetic-pharmacodynamic relationship of the selective serotonin reuptake inhibitors. Clin Pharmacokinet. 1996; 31:444-469.
55. Amsterdam JD, Fawcett J, Quitkin FMet al. Fluoxetine and norfluoxetine plasma concentrations in major depression: A multicenter study. Am J Psychiatry 1997; 154:963-969.
56. Caccia S, Fracasso C, Garattini S et al. Effects of short- and long-term administration of fluoxetine on the monoamine content of rat brain. Neuropharmacology 1992; 31:343-347.
57. Dailey JW, Yan, QS, Mishra PKet al. Effects of fluoxetine on convulsions and on brain serotonin as detected by microdialysis in genetically epilepsy-prone rats. J Pharmacol Exp Ther 1992; 260:533-540.
58. Hyttel J, Overø KF, Arnt J. Biochemical effects and drug levels in rats after long-term treatment with the specific 5-HT-uptake inhibitor, citalopram. Psychopharmacology 1984; 83:20-27.
59. Engberg G. Citalopram and 8-OH-DPAT attenuate nicotine-induced excitation of central noradrenaline neurons. J Neural Transm 1992; 89:149-154.
60. Akaoka H, Aston-Jones G. Indirect, serotonergic agonists attenuate neuronal opiate withdrawal. Neurosci 1993; 54:561-565.
61. Brady LS. Stress, antidepressant drugs and the locus coeruleus. Brain Res Bull 1994; 35:545-556.
62. Curtis AL, Valentino RJ. Corticotropin-releasing factor neurotransmission in locus coeruleus: A possible site of antidepressant action. Brain Res Bull 1994; 35:581-587.
63. Cusack B, Nelson A, Richelson E. Binding of antidepressants to human brain receptors: focus on newer generation compounds. Psychopharmacology 1994; 114:559-565.

64. Jenck F, Moreau J-L, Mutel V et al. Evidence for a role of 5-HT_{1C} receptors in the antiserotonergic properties of some antidepressant drugs. Eur J Pharmacol 1993; 231:223-229.
65. Narita N, Hashimoto K, Tomitaka S et al. Interactions of selective serotonin reuptake inhibitors with subtypes of σ receptors in rat brain. Eur J Pharmacol 1996; 307:117-119.
66. Leonard BE. The potential contribution of sigma receptors in antidepressant actions. In: Skolnick P ed. Antidpressants: New Pharmacological Strategies. Totowa, New Jersey; Humana Press, 1997:159-172.
67. Mongeau R, De Montigny C, Blier P. Activation of 5-HT_3 receptors enhances the electrically evoked release of [^{3}H]noradrenaline in rat brain limbic structures. Eur J Pharmacol 1994; 256:269-279.
68. Suzuki M, Matsuda T, Asano S et al. Increase of noradrenaline release in the hypothalamus of freely-moving rat by postsynaptic 5-hydroxytrypamine$_{1A}$ receptor activation. Br J Pharmacol 1995; 115:703-711.
69. Blandina P, Goldfarb J, Walcott et al. Serotonergic modulation of the release of endogenous norepinephrine from rat hypothalamic slices. J Pharmacol Exp Ther 1991; 256:341-347.
70. Goldfarb J, Walcott J, Blandina P. Serotonergic modulation of L-glutamic acid-evoked release of endogenous norepinephrine from rat hypothalamus. J Pharmacol Exp Ther 1993; 267:45-50.
71. Feuerstein TJ, Herrting G. Serotonin (5-HT) enhances hippocampal noradrenaline (NA) release: evidence for facilitatory 5-HT receptors within the CNS. Naunyn-Schmiedeberg's Arch Pharmacol 1986; 333:191-197.
72. Kidd EJ, Laporte AM, Langlois K et al. 5-HT3 receptors in the rat central nervous system are mainly located on nerve fibres and terminals. Brain Res 1993; 612:289-298.
73. Allgaier C, Warnke P, Stangl AP et al. Effects of 5-HT receptor agonists on depolarization-induced [^{3}H]-noradrenaline release in rabbit hippocampus and human neocortex. Br J Pharmacol 1995; 116:1769-1774.
74. Luppi PH, Aston-Jones G, Akaoka H et al. Afferent projections to the rat locus coeruleus demonstrated by retrograde and anterograde tracing with cholera-toxin B subunit and Phaseolus vulgaris leucoagglutinin. Neuroscience 1995; 65:119-160.
75. Vertes RP, Kocsis B. Projections of the dorsal raphe nucleus to the brainstem: PHA-L analysis in the rat. J Comp Neurol 1994; 340:11-26.
76. Aston-Jones G, Shipley MT, Chouvet G et al. Afferent regulation of locus coeruleus neurons: Anatomy, physiology and pharmacology. Prog Brain Res 1991; 88:47-75.
77. Renaud B, Buda M, Lewis BD et al. Effects of 5,6-dihydroxytryptamine on tyrosine hydroxylase activity in central catecholaminergic neurons of the rat. Biochem Pharmacol 1975; 24:1739-1742.
78. Haddjeri N, de Montigny C, Blier P. Modulation of the firing activity of noradrenergic neurones in the rat locus coeruleus by the 5-hydroxytryptamine system. Br J Pharmacol 1997; 120:865-875.
79. Reader TA, Briere R, Grondin L et al. Effects of p-chlorophenylalanine on cortical monoamines and on the activity of noradrenergic neurons. Neurochem Res 1986; 11:1025-1035.
80. Ferron A. Modified coeruleo-cortical noradrenergic neurotransmission after serotonin depletion by PCPA: electrophysiological studies in the rat. Synapse 1988; 2:532-536.
81. Shiekhattar R, Aston-Jones G. Sensory responsiveness of brain noradrenergic neurons is modulated by endogenous brain serotonin. Brain Res 1993; 623:72-76.
82. Aston-Jones G, Akaoka H, Chariety P et al. Serotonin selectively attenuates glutamate-evoked activation of noradrenergic locus coeruleus neurons. J Neurosci 1991; 11:760-769.
83. Engberg G. A metabolite of buspirone increases locus coeruleus activity via α_2-receptor blockade. J Neural Transm 1989; 91-98.
84. Gorea E, Davenne D, Lanfumey L et al. Regulation of noradrenergic coerulean neuronal firing mediated by 5-HT_2 receptors: Involvement of the prepositus hypoglossal nucleus. Neuropharmacol 1991; 30:1309-1318.
85. Aston-Jones G, Shipley MT, Chouvet G et al. Afferent regulation of locus coeruleus neurons: anatomy, physiology and pharmacology. Prog Brain Res 1991; 88:47-75.

86. Hamamura T, Lee Y, Fujiwara Y et al. Serotonin1A receptor agonists induce Fos protein expression in the locus coeruleus of the conscious rat. Brain Res 1997; 759:156-159.
87. Done CJG, Sharp T. Biochemical evidence for the regulation of central noradrenergic activity by 5-HT_{1A} and 5-HT_2 receptors: Microdialysis studies in the awake and anaesthetized rat. Neuropharmacology 1994; 33:411-421.
88. Hajós-Korcsok É, McQuade R, Sharp T. Influence of 5-HT_{1A} receptors on central noradrenergic activity: Microdialysis studies using (±) MDL 73005EF and its enantiomers. Neuropharmacology 1999; 38:299-306.
89. Dalley JW, Mason K, Stanford SC. Increased levels of extracellular noradrenaline in the frontal cortex of rats exposed to naturalistic environmental stimuli: Modulation by acute systemic administration of diazepam or buspirone. Psychopharmacology 1996; 127:47-54.
90. Hajós-Korcsok É, Sharp T. 8-OH-DPAT-induced release of hippocampal noradrenaline in vivo: evidence for a role of both 5-HT_{1A} and dopamine D_1 receptors. Eur J Pharmacol 1996; 314:285-291.
91. Rasmussen K, Aghajanian GK. Effect of hallucinogens on spontaneous and sensory-evoked locus coeruleus unit activity in the rat: reversal by selective 5-HT2 antagonists. Brain Res 1986; 385:395-400.
92. Gorea E, Adrien J Serotonergic regulation of noradrenergic coerulean neurons: Electrophysiological evidence for the involvement of 5-HT_2 receptors. Eur J Pharmacol 1988; 154:285-291.
93. Chiang C, Aston-Jones G. A 5-hydroxytryptamine$_2$ agonist augments γ-aminobutyric acid and excitatory amino acid inputs to noradrenergic locus coeruleus neurons. Neurosci 1993; 54:409-420.
94. Done CJG, Sharp T. Evidence that 5-HT_2 receptor activation decreases noradrenaline release in rat hippocampus in vivo. Br J Pharmacol 1992; 107:240-245.
95. Ennis C, Kemp JD, Cox B. Characterization of inhibitory 5-hydroxytrypamine receptors that modulate dopamine release in the striatum. J Neurochem 1981; 36:1515-1520.
96. Muramatsu M, Tamaki-Ohashi J, Usuki C et al. 5-HT_2 antagonists and minaprine block the 5-HT-induced inhibition of dopamine release from rat striatal slices. Eur J Pharmacol 1988; 153:89-95.
97. Blandina P, Goldfarb J, Craddock-Royal B et al. Release of endogenous dopamine by stimulation of 5-hydroxytryptamine$_3$ receptors in rat striatum. J Pharmacol Exp Ther 1989; 251:803-809.
98. Yadid G, Pacak K, Kopin IJ et al. Endogenous serotonin stimulates striatal dopamine release in conscious rats. J Pharmaol Exp Ther 1994; 270:1158-1165.
99. Galloway MP, Suchowski CS, Keegan MJ et al. Local infusion of the selective 5-HT-1b agonist, CP-93,129 facilitates striatal dopamine release in vivo. Synapse 1993; 15:90-92.
100. Chen N-H, Reith MEA. [^{3}H]Dopamine and [^{3}H]serotonin release in vitro induced by electrical stimulation in A_9 and A_{10} dopamine regions of rat brain: Characterization and responsiveness to cocaine. J Pharmacol Exp Ther 1993; 267:379-389
101. Jacocks HM, Cox BM. Serotonin-stimulated release of [^{3}H]dopamine via reversal of the dopamine transporter in rat striatum and nucleus accumbens: A comparison with release elicited by potassium, N-methyl-D-aspartic acid, glutamic acid and D-amphetamine. J Pharmacol Exp Ther 1992; 262:356-364..
102. Parsons LH, Justice JB. Perfusate serotonin increases extracellular dopamine in the nucleus accumbens as measured by in vivo microdialysis. Brain Res 1993; 606:195-199.
103. Yi S-J, Gifford AN, Johnson KM. Effect of cocaine and 5-HT_3 receptor antagonists on 5-HT-induced [^{3}H]dopamine release from rat striatal synaptosomes. Eur J Pharmacol 1991; 199:185-189.
104. Simon JR, Ghetti B. Is there a significant somatodendritic uptake of dopamine in the substantia nigra? Evidence from the weaver mutant mouse. Neurochem Int 1993; 22:471-477.
105. Carboni E. Tanda GL, Di Chiara G. Blockade of the noradrenaline carrier increases extracellular dopamine concentrations in the prefrontal cortex: Evidence that dopamine is taken up in vivo by noradrenergic terminals. J Neurochem 1990; 55:1067-1070.

106. Chen J, van Praag HM, Gardner EL. Activation of 5-HT_3 receptor by 1-phenylbiguanide increases dopamine release in the rat nucleus accumbens. Brain Res 1991; 543:354-357.
107. Chen J, Paredes W, van Praag H et al. Presynaptic dopamine release is enhanced by 5-HT receptor activation in medial prefrontal cortex of freely moving rats. Synapse 1992; 10:264-266.
108. Benloucif S, Keegan MJ, Galloway MP Serotonin-facilitated dopamine release in vivo: Pharmacological characterization. J Pharmacol Exp Ther 1993; 265:373-377.
109. Bonhomme N, de Deurwaèrdere P, Le Moal N et al. Evidence for 5-HT_4 receptor involvement in the enhancement of striatal dopamine release induced by serotonin: A microdialysis study in the halothane-anesthetized rat. Neuropharmacology 1995; 34:269-279.
110. Steward LJ, Ge J, Stowe RL et al. Ability of 5-HT_4 receptor ligands to modulate rat striatal dopamine release in vitro and in vivo. Br J Pharmacol 1996; 117:55-62.
111. Nurse B, Russell VA, Taljaard JJF. Characterization of the effects of serotonin on the release of [^{3}H]dopamine from rat nucleus accumbens and striatal slices. Neurochem Res 1988; 13:403-407.
112. De Belleroche JS, Bradford HF. Presynaptic control of the synthesis and release of dopamine from striatal synaptosomes: A comparison between the effects of 5-hydroxytryptamine, acetylcholine and glutamate. J Neurochem 1980; 35:1227-1234.
113. De Deurwaerdère P, Bonhomme N, Lucas G et al. Serotonin enhances striatal dopamine outflow in vivo through dopamine uptake sites. J Neurochem 1996; 66:210-215.
114. Schmidt CJ, Black CK. The putative 5-HT_3 agonist phenylbiguanide induces carrier-mediated release of [^{3}H]dopamine. Eur J Pharmacol 1989; 167:309-310.
115. Prisco S, Pagannone S, Esposito E. Serotonin-dopamine interaction in the rat ventral tegmental area: An electrophysiological study in vivo. J Pharmacol Exp Ther 1994; 271:83-90.
116. Yoshimoto K, McBride WJ. Regulation of nucleus accumbens dopamine release by the dorsal raphe nucleus in the rat. Neurochem Res 1992; 17:401-407.
117. Beasley CM, Masica DN, Potvin JH Fluoxetine: a review of receptor and functional effects and their clinical implications. Psychopharmacology 1992; 107:1-10.
118. Fozard JR, Mwaluko GMP. Mechanism of the indirect sympathomimetic effect of 5-hydroxytryptamine on the isolated heart of the rabbit. Br J Pharmacol 1976; 57:115-125.

Chapter 11

The Mechanism of Action of SSRIs: A New Hypothesis

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The introduction of the selective serotonin reuptake inhibitors (SSRIs) into medical treatment in the 1980s revolutionized psychiatric practice and fueled the interest in the role of serotonin (5-hydroxytryptamine, 5-HT) in the underlying neurobiology of the psychiatric disorders. In reviewing the literature, one is struck by a curious and interesting dichotomy between the fairly selective effect that these drugs have on the serotonergic system and the remarkably 'non-selective' manner in which they are used clinically. In actuality, these compounds vary considerably regarding their relative 'selectivity' for 5-HT reuptake, and some SSRIs have significant action on other biogenic amine neurotransmitter systems (for further details: see Chapter 10). However, there is no doubt that the SSRIs are a marked and significant improvement on our previous attempts to selectively increase 5-HT neurotransmitter function with precursors such as tryptophan. Certainly, the SSRIs are far more selective, as a class, than the previously available tricyclic antidepressants (TCAs).

The SSRI's remarkably broad spectrum of utility, crossing (and blurring) diagnostic boundaries of depressive disorders, panic disorder, obsessive-compulsive disorder, bulimia, post-traumatic stress disorder, premenstrual dysphoric disorder and, no doubt, other conditions, raises important and potentially controversial questions regarding the utility, if not outright validity, of contemporary diagnostic terminology, presently codified in DSM-IV. In some respects, this promotes a degree of diagnostic nihilism, similar to the scenario in American psychiatry in the pre-psychopharmacologic era, when psychoanalysis was widely regarded as an effective treatment of choice for most, if not all, neurotic patients, regardless of precise diagnosis. In other words, if the treatment works, independent of diagnosis, why bother to diagnose at all? A new diagnostic scheme may evolve from clinical experience and further neurobiological research, in which we might diagnose 'serotonin (5-HT) deficit disorder,' rather than the clinically descriptive, criterion-driven diagnostic schemes in vogue today. Thus, from both clinical and theoretical perspectives, the SSRIs have, and will continue to, revolutionize psychiatry.

Within this context and framework of reference, we will outline the current state of understanding of the mechanism of action of these important and unique medications. In particular, we will focus on some new findings in preclinical research. Also, the SSRIs are contrasted and briefly compared with other types of antidepressants. We will discuss issues of neuroanatomy of serotonergic function which might account for the relief of a wide variety of symptoms and effects on several behaviors. Also, the efficacy of the SSRIs in premenstrual dysphoric disorder provides a potentially important model for their action in depressive states. Finally, we provide a proposed rationale for the broad spectrum of action

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of the SSRIs in the context of a new and unifying hypothesis of brain homeostasis, neurotransmitter interactions and dimensions of psychopathology.

Serotonergic Neurotransmission

5-HT is an indoleamine neurotransmitter with widespread distribution in the brain and significant projections to all limbic structures. It exerts tonic and inhibitory influence by actually increasing the threshold for neural response and is involved in modulating a variety of brain functions, including: sleep, appetite, libido, fear, pain, sensory input and motor expression. In mammalian brain, 5-HT is found in neurons whose cell bodies lie in the dorsal and median raphé nuclei located in the pons and medulla. The amygdala, hypothalamus, basal ganglia, primary and association-receiving areas and frontal lobe are innervated by the more discretely organized dorsal raphé serotonergic cell bodies. The median raphé is more diffusely organized and exerts a nonspecific and global influence on arousal and excitability by innervating the hippocampus, cingulate gyrus, and septum. With this complex and dual organization, the dorsal raphé and the median raphé can exert quite different effects simultaneously and thereby engage in perceptual filtering in multiple brain regions (reviewed in ref. 1). In addition, the serotonergic and noradrenergic systems interact in the modulation of arousal, sleep, emotional processing and pain.

5-HT is synthesized from the essential amino acid precursor, tryptophan, and packaged into synaptic vesicles. The vesicles release their contents into the synapse in response to depolarizing stimuli and subsequently elicit pre- and postsynaptic responses through the activation of one of many subtypes of 5-HT receptors. Subsequently, 5-HT is cleared from the extracellular space by uptake transporter proteins localized in the plasma membranes of presynaptic terminals.

These uptake sites are the target of the SSRI blockade. With the uptake transporter clearance inhibited, extracellular levels of 5-HT remain elevated longer and can exert a greater effect postsynaptically. This effect is not limited to postsynaptic effects and typically happens acutely to a greater extent at the somatodendritic area rather than at the axon terminals (reviewed in ref. 2; see also Chapter 9). Greater 5-HT concentrations in the synaptic cleft in this area also activate the presynaptic autoreceptor which decreases presynaptic 5-HT release. These considerations could have some clinical relevance in regard to the delayed onset of therapeutic action of SSRIs, since the combined use of a 5-HT ($5HT_{1A}$ and $5\text{-}HT_{1B}$) autoreceptor antagonist and an SSRI in the treatment of depression is hypothesized to accelerate the onset of therapeutic response to SSRIs. Another finding in regard to the 5-HT presynaptic autoreceptors is that long-term administration of antidepressant drugs, including the SSRIs, tends to decrease the responsiveness of these autoreceptors and thus bring about a net increase in 5-HT neurotransmission at the terminal axon. This desensitization of 5-HT autoreceptors reportedly occurs over a delayed time course, whereas the uptake inhibition is immediate. Finally, the last step for SSRI mechanism of action is the desensitization of postsynaptic receptors. The delay in a combined receptor effect may explain the 2-4 week time until onset of therapeutic efficacy of the SSRIs.

Within the past 5 years, radioligand binding studies and molecular cloning techniques have identified some eight subtypes of 5-HT receptors, each with extraordinarily diverse electrophysiological actions. A detailed description of 5-HT receptor subtypes is readily available elsewhere[3,4] and is beyond the scope of this chapter. The major point to be made is that the SSRI focus of action at the uptake transporter site is an initial step in the complex action of serotonergic neuroregulation. Once 5-HT concentrations are elevated in the synapse, a diverse array of postsynaptic effects can proceed. This may in part explain the broad spectrum of action of SSRIs. Hence, because of this diversity, as we continue to decipher

the postsynaptic serotonergic neuroregulation involved in various psychiatric syndromes, even more precise and 'selective' treatments may potentially develop.

Preclinical Models of Depression and Relationship with 5-HT

One approach to understanding the behavioral effects and mechanism of action of SSRIs involves study of animal models of human psychopathology. An established and valid animal model of depression, extensively studied by our laboratory, is 'learned helplessness' which is a stress-induced behavioral depression. The basic paradigm involves an exposure, usually of rats, to uncontrollable, inescapable stress followed by a subsequent test, usually involving a task in which the stress can be terminated by the animal. An attractive aspect of the learned helplessness model is that not all animals develop learned helplessness after inescapable stress (just as not all humans become depressed following stressful life events). This variability in outcome after stress, considered a possible model for 'coping,' allows comparisons to be made between animals that receive identical stress but have different behavioral reactions to stress: helpless versus non-helpless. Animals with learned helplessness exhibit a number of behaviors similar to the signs of depression in humans. For example, learned helpless rats have decreased food intake, weight loss, motor retardation, decreased exploratory behavior and sleep/wake cycle disturbance. The extent to which learned helplessness in the rat is a model of depression in humans is problematic, since many depressive episodes in humans are not clearly preceded by a severe and inescapable stressor.

The resultant performance and behavioral deficits associated with prior inescapable stress respond to antidepressant drugs with remarkable specificity, but only when these agents are administered over several days, similar to the time lag required for the response in clinical depression.[5] Furthermore, anxiolytic drugs are active in the learned helplessness model, in preventing the development of behavioral depression if administered prior to stress exposure. Anxiolytics will not reverse or 'cure' helpless behavior if administered after stress exposure. Thus, learned helplessness suggests that an element of anxiety is required for the development of depression. Also, it suggests that, in some aspects, the neuropharmacological mechanisms involved in preventing depressive episodes may be different from the mechanisms involved in reversing depression and returning the organism to homeostasis.

Use of behavioral models such as learned helplessness in studying serotonergic function provides a valuable dimension in examining SSRIs and their effects on brain function. The learned helplessness animal model may be a useful test of the effects of antidepressant and anxiolytic medications in their ability to prevent or reverse learned helplessness behavior associated with inescapable stress. In the case of the SSRIs, whose clinical spectrum of efficacy covers both anxiety and depression, the learned helplessness animal model may provide useful insights regarding how serotonergic function influences behavior.

Learned Helplessness and 5-HT

5-HT plays a major role in learned helplessness.[6,7] Briefly, micro-injection of 5-HT into the medial prefrontal cortex reverses established helpless behavior and does so on an acute basis. That is to say, repeated injections over several days are not required for behavioral activity. Interestingly, micro-injection of a TCA had the same effect, suggesting a serotonergic mechanism for their behavioral action. Further support for this idea is derived from in vivo microdialysis experiments which showed that chronic treatment with a TCA, acute administration of a benzodiazepine, or behavioral training all prevented helplessness in conjunction with their effects in maintaining 5-HT in the extracellular space similar to control values. Additionally, all three methods of preventing helplessness preserved intraneuronal stores of 5-HT and prevented their depletion by inescapable stress.[6] Thus, in

the cortex, intraneuronal depletion of 5-HT correlates with depressed behavior, and various seemingly different methods of preventing learned helplessness seemed to share a serotonergic mechanism.

The complexity of 5-HT's roles in learned helplessness is highlighted by our research using quantitative autoradiography.[8] This technique revealed that in cortex, down-regulation of the 5-HT reuptake site, measured with [^{3}H]paroxetine binding, characterized rats subjected to inescapable stress, regardless of whether they became helpless or not. A lower density of reuptake sites might relate to increased concentrations of extracellular 5-HT.

We have studied the effect of SSRIs in the learned helplessness model. Fluvoxamine administered repeatedly for 5 days prior to stress prevented the development of learned helplessness. Interestingly, the baseline extracellular levels of 5-HT in the medial prefrontal cortex were increased in the fluvoxamine treated rats, while the intraneuronal 5-HT was similar to non-stressed controls. This finding was different from that with imipramine which did not alter the baseline 5-HT levels in the extracellular space, perhaps due to its lower affinity for the 5-HT reuptake site, compared to fluvoxamine (unpublished data).

5-HT is functionally related to learned helplessness in several other brain regions as well. In dorsal hippocampus, we found that the density of the 5-HT$_2$ receptor was significantly decreased in rats that received inescapable stress and did not become helpless, compared to those that did develop learned helplessness, and compared to control.[8] Perhaps paradoxically, micro-injection of the antisense oligonucleotide related to the 5-HT$_2$ receptor into dorsal hippocampus was reported to cause helpless behavior in naïve, non-stressed rats.

Of course, the effects of SSRIs on the serotonergic system are not limited merely to inhibiting reuptake at the transporter sites on the presynaptic terminal. In addition to presynaptic 5-HT autoreceptor desensitization, changes in postsynaptic 5-HT receptors are also described with SSRIs; postsynaptic 5-HT$_2$ receptors are located throughout the hippocampus and cortex and adapt to chronic activation by reducing response sensitivity or receptor density, ('down-regulating'). Paradoxically, these receptors are also down-regulated following chronic administration of 5-HT antagonists.[4] An up-regulation of 5-HT$_2$ binding sites has been reported in major depression.[9] Following chronic SSRI administration, the 5-HT$_2$ potentiation diminishes by a reduction in receptor density, consistent with 5-HT$_2$ receptor adaptation. Although not all SSRIs down-regulate or desensitize the 5-HT$_2$ receptor, this effect is thought to be an essential part of the SSRI mechanism of action. The down-regulation we found in the dorsal hippocampus of rats that had received inescapable stress without becoming helpless suggests this may represent a natural adaptive mechanism for 'coping' with stress.

Another brain region where 5-HT plays a functional role in learned helplessness is the septum.[10] Micro-injection of 5-HT into this brain region both prevented and reversed learned helplessness. In synaptosomes from septum, helpless rats had decreased 5-HT release, and repeated (but not acute) administration of TCAs led to increased 5-HT release. Rats that had received inescapable stress, followed by repeated antidepressant administration, which normalized behavior, also had septal serotonergic activity similar to control. Thus, in this region, as well as in medial prefrontal cortex, there is a clear association of 5-HT function with behavior. Using in vivo microdialysis, we recently studied release of 5-HT and its metabolite, 5-hydroxyindole acetic acid (5-HIAA) in the septum (unpublished data). Levels of 5-HIAA were elevated in the perfusate from rats that received inescapable stress but did not become helpless, while 5-HT levels in microdialysis perfusates were no different in helpless, non-helpless, or control rats. This suggests, that an increase in 5-HT metabolism or turnover may correlate with maintenance of normal, non-depressed behavior.

Behaviorally, there are subtle differences between the SSRIs and the TCAs. In our laboratory, though we have not completed an exhaustive comparative study of all the available

SSRIs at multiple doses, the behavioral effects of SSRIs in preventing learned helplessness appear somewhat less robust than those of the tricyclics. In other laboratories,[11] using a somewhat different behavioral protocol for learned helplessness, SSRIs and tricylics demonstrated comparable effects on helpless behavior, but only under a dramatically different schedule for drug injections for each compound. We do not know the extent to which these preclinical differences are related to clinical differences between these two classes of drugs, if at all.

It is probably worth reiterating that the SSRIs are relatively, not absolutely, selective for 5-HT, since some of these agents have appreciable effects on other neurotransmitters as well. Interestingly, newer in vivo studies suggest different biogenic amine reuptake blockade profiles for the SSRIs than those reported by the earlier receptor binding studies (see also: Chapter 10). Since in vivo studies examine the brain as a whole, with neuronal connections intact, they may be a more accurate reflection of actual brain-drug interaction than studies of post-mortem tissue. Using in vivo microdialysis, we showed fluoxetine to increase extracellular levels of both noradrenaline and dopamine similar to imipramine, whereas fluvoxamine had negligible effects on the catecholamine neurotransmitters.[12] Of course, the extent to which these factors influence therapeutic effects or adverse effects is not known, and may be irrelevant.

What conclusions may be made from these facts? First, the interaction between drugs, brain chemistry and behavior is extraordinarily complex. We can no longer conceptualize psychiatric syndromes as deficit states of one or another neurotransmitter. The behavioral syndrome referred to as 'depression' in humans or 'learned helplessness' in rodents correlates with complex changes in 5-HT receptors and levels, both within and outside the neurons, that depend on brain region. The changes in serotonergic function caused by SSRIs in naïve, normal control brain are different from those caused in a behaviorally disordered brain. Finally, the changes in 5-HT caused by SSRIs that are functionally related to behavioral improvement are only now beginning to be deciphered and elucidated. These can be conceptualized as behaviors that are mediated via neural networks and systems with multiple, regionally-specific neurotransmitter interactions playing a major role in elucidating mental function. Figure 11.1 illustrates the hypothetical neuronal networks involved in learned helplessness, which offer a starting point in the understanding of the behavioral neurochemistry of mood and anxiety disorders.

Comparison of SSRIs and Other Antidepressant Agents

The TCAs inhibit 5-HT, noradrenaline and dopamine uptake sites and other sites, such as histaminergic, adrenergic, muscarinic, and dopaminergic receptors. The TCAs have individual differences in receptor affinity profiles. Most of the SSRIs do not inhibit the histaminergic or adrenergic sites to any clinically significant level. Activity at the muscarinic receptor is negligible for fluoxetine, fluvoxamine, citalopram and sertraline. However, paroxetine has some muscarinic receptor activity and thus, an increased potential for anticholinergic side-effects. These receptor affinity differences explain the lower side-effect profiles for the SSRIs compared with the TCA medications. However, as noted, receptor affinities obtained from post-mortem tissue binding experiments may not reflect in vivo brain effects.

Tricyclic antidepressants have also been shown to reduce the sensitivity of 5-HT_{1A} receptors. However this may occur postynaptically rather than at the terminal autoreceptor. The difference in loci of influence at the receptor level may explain why some patients respond to one class of antidepressants as opposed to another.

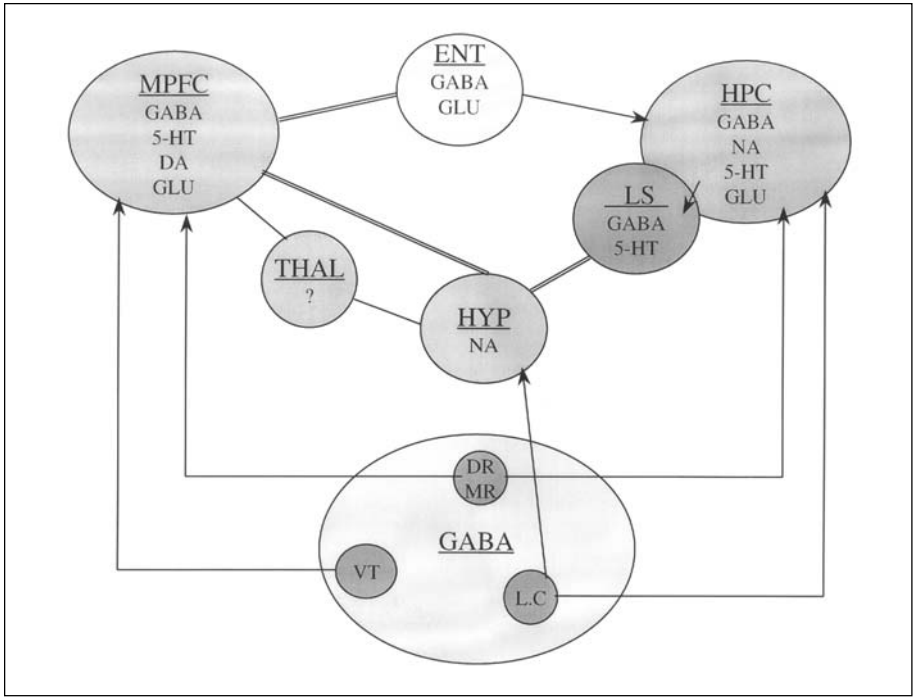

Fig. 11.1. Abbreviations: DR, dorsal raphe; LC, locus coeruleus; VTA, ventral tegmental area. This hypothetical framework explains the roles of the biogenic amine neurotransmitters, dopamine (DA), noradrenaline (NA) and serotonin (5-HT), as well as the amino acid neurotransmitters GABA and glutamate (GLU), in the neurochemistry of learned helplessness. Also, the behavior is conceptualized as involving multiple brain regions of the limbic system and related areas including medial prefrontal cortex (MPFC), entorhinal cortex (ENT), hippocampus (HPC), lateral septum (LS) and hypothalamus (HYP). The central role of 5-HT in medial prefrontal cotex in development and reversal of learned helplessness is apparent. The learned helplessness model is a paradigm for 'stress dysfunction disorders' and provides an experimental model for studying the relationships between anxiety and depression.

SSRI Spectrum of Therapeutic Action

The efficacy of SSRIs in the treatment of major depression, panic disorder, and obsessive-compulsive disorder has clearly been demonstrated. In addition, data is accumulating on the therapeutic effects of SSRIs in conditions of obesity, eating disorders, post-traumatic stress disorder, social phobia, premenstrual dysphoric disorder and trichotillomania. How can one class of medications work for such a seemingly diverse group of illnesses? Are these agents in fact nonspecific and work as a steroid might for a multitude of inflammatory conditions? Or alternatively, is there an underlying psychopathology, relating to 5-HT, that represents a common neurochemical theme among these conditions? Our methods of classification in psychiatry are clinical and descriptive and may relate poorly to actual brain function.

Monoamine and Brain Homeostasis: A New Hypothesis in Understanding Psychiatric Disorders

The simplistic monoamine depletion hypothesis as an explanation for major depression or any psychiatric disorder is rapidly undergoing critical re-evaluation and restructuring. Of course, it is illogical to think that one neurotransmitter is responsible for one diagnostic category. In addition, our categorical style of making diagnoses is imperfect. Perhaps major depressive disorder is the end-stage syndrome with a multitude of originating etiologies, both psychological and physiological. In addition, there is overlap, not only in illness comorbidity, but also overlap with one individual illness symptomatology and another based on DSM-IV criteria. A good example is major depressive disorder and post-traumatic stress disorder (PTSD). Both illnesses indeed frequently occur together in the same patient. Even though the criteria may seem to separate these diagnoses, in real clinical practice, it is unusual to make the diagnosis of PTSD in a treatment-seeking patient without also diagnosing major depression, given the extreme overlap in DSM-IV criteria. What do anxiety disorders and mood disorders have in common? Can it be that they are more similar than different and the specific symptom profile reflects different stages in the course or evolution of illness?

Indeed, a common clinical phenomenon is that what begins as an anxiety disorder typically evolves into a depressive disorder. In fact, patients with obsessive-compulsive disorder develop major depression in 95% of cases, with post-traumatic stress disorder in about 85% of cases, and with panic disorder in over 50% of cases.[13] The converse is not generally true. In other words, patients who begin their psychiatric morbidity with a diagnosis of major depressive disorder do not tend to proceed to develop panic disorder or obsessive-compulsive disorder in any great proportion. Thus, in many patients, depression and anxiety represent different phases of the same disease process. This may help to explain the similarities in clinical findings of serotonergic abnormalities in patients' anxiety and mood disorders prior to treatment, and the therapeutic response of patients with anxiety and mood disorders to serotonergic agents.

Biological Abnormalities in 5-HT and Theories of Depression

We have discussed how and whether animal models of stress-induced depression can provide insights into serotonergic function correlated with depression and into the mechanisms of action of SSRIs. To what extent do clinical research findings in humans support the animal data? Of course, biological abnormalities in the symptomatic depressed state include a range of disturbances in noradrenergic, serotonergic, dopaminergic, and GABAergic neurotransmitter systems, as well as secondary effects in several neuroendocrine systems.[14] The complex dynamic interactions and inter-regulation of neurotransmitter systems suggest that it is more important to consider the relative balance of neurotransmitters than their absolute independent effects. Much pharmacological data also supports the concept of biological heterogeneity in depression, evidenced by the fact that some patients respond primarily to antidepressants acting principally on the noradrenergic system, while others respond preferentially to serotonergic antidepressants. In fact, biologic heterogeneity between and within depressive subtypes represents a contemporary hallmark of most current research and literature. Thus, serotonergic dysfunction has not been consistently demonstrated in most patients with depressive disorders. Though serotonergic hypotheses of depression have been formulated and reformulated for well over 30 years, in the past, most evidence supporting these hypotheses derives from preclinical data on drug actions, and from indirect measurements of central 5-HT function in humans. However, new clinical data, described below, strongly supports the concept that regional cerebral serotonergic function is abnormal in depression.

A Role for 5-HT in Depression

Serotonergic neurons play a key role in the modulation, organization and coordination of appropriate responses to a wide variety of stimuli. As noted, 5-HT acts primarily as an inhibitory neurotransmitter, has a significant role in several behaviors that are consistently disturbed in many persons with depression (e.g., mood, sleep, sexual activity, appetite, circadian and seasonal rhythms, neuroendocrine functions, body temperature, motor activity, and cognitive function).[14-17] Studies suggesting that 5-HT function is abnormal in depression have revealed: 1) decreased brain concentration of 5-HT and decreased CSF concentrations of 5-HIAA; 2) alterations of both presynaptic and postsynaptic CNS serotonergic receptors; 3) alterations in putative peripheral markers of CNS serotonergic function such as platelet 5-HT uptake, platelet [^{3}H]imipramine or [^{3}H]paroxetine binding, platelet 5-HT_2 receptor density, and whole blood 5-HT content; and 4) receptor abnormalities in post-mortem brain tissue of depressed patients and suicide victims including increased density of 5-HT_2 binding sites, decreased number of 5-HT transporter binding sites, and increased postsynaptic 5-HT_{IA} and 5-HT_2 receptor binding. However, each of these findings is limited by either having been difficult to replicate, or being an indirect measure of brain 5-HT function.

The other major line of indirect evidence for a 5-HT theory in depression is the fact that virtually all somatic antidepressant drugs, regardless of their receptor affinity in binding studies, have been shown to increase the efficacy of brain serotonergic neurotransmission. The specific agents do so by several different mechanisms, including increasing the sensitivity of postsynaptic 5-HT_{IA} and 5-HT_2 receptors or by reducing the function of presynaptic and somatodendritic autoreceptors. The net result of enhanced serotonergic neurotransmission in most limbic structures, such as amygdala and hippocampus, is reduced neuronal firing. Further, in patients treated with serotonergic antidepressants who exhibit a remission, rapid depletion of 5-HT results in a prompt clinical relapse. For example, Delgado et al[18-20] have reported that decreasing the availability of tryptophan, the precursor of 5-HT, can induce mild dysphoria in healthy, non-depressed persons. It also induces a rapid, clinically significant and transient reversal of the effect of the antidepressant medication in recovering medicated patients with major depression. Finally, all known SSRIs are clinically effective antidepressant medications.

The status of 5-HT receptors in patients with depression are of particular relevance. Some receptor-specific challenge data showing blunted responses to 5-HT_1 probes have been interpreted as indicative of down-regulated postsynaptic 5-HT_{IA} receptors. However, as indicated above, data from suicide victims indicates down-regulated transporter activity and up-regulated postsynaptic 5-HT_{1A} and 5-HT_2 receptors. Postsynaptic 5-HT_{1A} receptors inhibit neuronal firing, while postsynaptic 5-HT_2 receptors are thought to generally enhance it. Since these two receptor subtypes co-exist in the amygdala, hippocampus, some thalamic nuclei, and cortex, all areas implicated in the neurobiology of depression, the net effect of depleted synaptic 5-HT in the disease state or enhanced synaptic 5-HT in the challenged or treated state will be determined by the functional balance between 5-HT_{IA} and 5-HT_2 receptor subtypes. Because the anatomical distribution of 5-HT systems is diffuse, the functional neuroanatomy of net effects is difficult to predict.

Maes and Meltzer[21] concluded that the current evidence supports the hypothesis that a deficit in serotonergic activity is a proximate cause of depression and that a deficit in serotonergic activity is important as a vulnerability factor in depression. They recommend further studies with specific 5-HT_{1A} and 5-HT_{2A} or 5-HT_{2C} ligands, and challenge studies using brain imaging with single photon emission computerized tomography (SPECT) or positron emission tomography (PET) to clarify the 5-HT abnormality in depression.

Functional Brain Imaging Studies of the Serotonergic System in Depression

Few data exist regarding direct imaging of 5-HT receptors in depressed subjects. Mayberg et al,[22] using PET imaging of methylspiperone, found that patients after right, but not left-sided strokes had greater ipsilateral than contralateral abnormality in 5-HT_2 receptors in undamaged temporal and parietal regions. Additionally, in subjects with left-sided strokes, the ipsilateral/contralateral temporal lobe 5-HT_2 receptor ratio correlated inversely with depression scores, suggesting that a failure to up-regulate ipsilateral 5-HT_2 receptors after left-sided strokes could be related to the development of depression. D'Haenen et al,[23] utilizing ketanserin as a 5-HT_2 receptor ligand imaged by SPECT, reported higher uptake of the tracer in the parietal cortex of patients with depression. They also noted asymmetry (right greater than left) in the infero-frontal region in depressed subjects and not in control subjects, thus indicating a 5-HT_2 receptor change in major depression.

Grasby et al [24] evaluated regional cerebral blood flow (rCBF) before and after oral administration of buspirone (30 mg) or placebo in normal controls under two conditions (5 word-learning and 15 word-learning) and found that buspirone induced increased rCBF in the cuneus during both tasks. However, decreased rCBF seen in the dorsolateral prefrontal cortex and cingulate cortex was present only during the 5 word task but not during the 15 word task. Unfortunately, the authors did not measure the rCBF response to buspirone challenge alone. Two important issues, therefore, emerge from this study, namely that the effects of buspirone on rCBF were not bilaterally uniform, and did not include the entire distribution of high density areas of the 5-HT_{1A} receptor system. The interaction between the response of the pharmacological challenge and various cognitive and behavioral tasks performed during the challenge needs further elaboration.

Mann et al,[25,26] using a *d,l*-fenfluramine challenge with PET scanning, found significant changes in 6 normal controls. They observed increases in regional cerebral glucose metabolism in the left prefrontal (inferior, middle and superior frontal gyri and anterior cingulate) and left temperoparietal cortex. Some decreases were observed in the right hemisphere. In contrast, subjects with major depression had no response. Blunting of the normal response was seen as support for the 5-HT hypothesis of depression. The laterality of response in normal subjects suggested that the failure in depressed subjects was purely left-sided (neither group showed an appreciable right-sided response to *d,l*-fenfluramine), and was interpreted as being consistent with other data demonstrating left prefrontal abnormalities in depression. The samples were small (N = 6), included subjects of both genders, and the age range was not restricted, so interpretive caution is required. Finally, the prolactin response was not different between the two groups, reiterating the fact that in vivo neuroimaging is likely to be more sensitive than indirect measures of central 5-HT function.

Kapur et al[27] used the *d,l*-fenfluramine challenge with PET to measure [^{18}fluro]deoxy-glucose (FDG) uptake in 11 normal subjects during an auditory/cognitive challenge. They found relative increases in metabolism in the prefrontal cortex (Broadman areas 45, 46, 47 and 10) and a relative decrease in the occipital-temporal cortex (Broadman areas 18, 19 and 37) during serotonergically-enhanced cognitive responses compared to cognitive challenge alone. A left temporo-insular cortical decrease following *d,l*-fenfluramine was also observed.

In summary, recent data from direct measures of 5-HT function in humans supports an important role for 5-HT in depression, with anatomical specificity. A major challenge for future research will be to investigate the congruence and divergence between clinical and preclinical data. Though the extent to which animal models can model human mental illness is questioned, brain structures most implicated in human depression, such as medial prefrontal cortex, septum, amygdala, hippocampus, and hypothalamus, are also the most implicated in rat models of learned helplessness. Future research should focus on molecular

and micro-architectural aspects of 5-HT function in depression, and the effects of the SSRIs on these factors.

Premenstrual Dysphoric Disorder and 5-HT

An interesting, and potentially important, model for the serotonergic balance theory of mood stability is found in premenstrual dysphoric disorder (PMDD). This condition, though often trivialized by the lay press, is a mental illness, often disabling, and occasionally life-threatening. The current psychiatric diagnostic category for severe premenstrual syndrome (PMS), PMDD, is categorized in DSM-IV as a 'Depressive Disorders Not Otherwise Specified,' in recognition of its close relationship with other mood disorders.

Symptoms that are seen in PMDD, and are required for the diagnosis, include low mood, mood swings, tension and irritability during the late luteal phase of the menstrual cycle. Thus, PMDD is a primarily psychiatric or behavioral condition, and the diagnosis is not used to describe women who suffer from only physical premenstrual symptoms, such as breast pain and bloating, even though these may be severe. There is a close relationship between PMDD and major depressive disorder, since 30% of women who suffer from PMDD have a prior history of major depression.[28] Also, women with PMDD are at greater risk for eventually developing major depression, even if they have not had antecedent depression.[29] Thus, PMDD represents a mood disorder with a clear and predictable physiological etiology, and, as such, a potential model for research.

A number of biological investigations including patients who suffer from PMS as well as PMDD have linked the pathophysiology of these severe premenstrual disorders to 5-HT.[30] Older studies investigating platelet [^{3}H]5-HT reuptake in women suffering from PMS have found that luteal phase platelet [^{3}H]5-HT reuptake is decreased in women suffering from either PMS or PMDD.[31,32] However, there are several studies which have failed to confirm this finding.[33,34] Using the ligand [^{3}H]imipramine to explore 5-HT reuptake, one research group found reduced binding sites in PMDD women compared to controls during the early luteal phase, while a second study reported increases in PMDD women during both phases of the cycle, although statistical significance was attained only during the follicular phase.[35] Although the majority of studies suggest a decrease in the number of 5-HT reuptake sites in women with PMS or PMDD, there are some inconsistencies which may be due to the ways in which patients were diagnosed as well as the various time points during the menstrual cycle during which uptake was investigated.

Primate data suggest that low 5-HT is associated with changes in sleep, appetite and irritability. Given these findings, Rapkin[36] investigated levels of whole blood 5-HT in women with severe premenstrual dysphoria compared to controls. It was found that symptomatic women had lower levels of whole blood 5-HT than asymptomatic controls. The induction of low plasma levels of 5-HT through a paradigm of tryptophan depletion supports these earlier findings. Menkes and colleagues[37] administered a neutral amino acid cocktail low in tryptophan to women with PMDD and controls during both times of the menstrual cycle. Theoretically this depletion of the 5-HT precursor, tryptophan, should lead to lower central 5-HT levels.[19] Menkes and colleagues[37] found that depletion of tryptophan was more likely to provoke premenstrual symptoms in women with PMDD than controls. Symptom provocation occurred during both the luteal and follicular phase, although it was more evident during the follicular phase when symptoms are normally low.[37] Unpublished data from a second site confirms the capacity of tryptophan depletion to provoke symptoms in PMDD women (Halbreich, personal communication). A recently presented study found that the strength of the amino acid cocktail (i.e., greater concentration of neutral amino acids) was correlated with tryptophan depletion and symptom provocation.[38] Thus, women with PMDD who drank a 100 g cocktail of neutral amino acids without tryptophan had

greater depletion and more symptoms than women with PMDD who drank a 50 g cocktail of neutral amino acids without tryptophan. These three studies support a role for lower functional 5-HT levels in women with PMS or PMDD; certainly the artificial lowering of peripheral and central tryptophan levels leads to symptom provocation.

Neuroendocrine challenge provides another method for probing the integrity of the serotonergic system in PMDD women. Administration of tryptophan to women with PMDD produced a blunted growth hormone and cortisol response compared to the response found in control women. These differences were detected during both phases of the menstrual cycle,[39] suggesting that trait differences exist between PMDD patients and controls. When the prolactin response to tryptophan administration was evaluated, blunting occurred only during the premenstrual phase in this same group of symptomatic women. The more selective 5-HT_{1A} partial agonist, buspirone, also led to a blunted prolactin response in PMDD patients compared to controls.[40] However, women were tested only during the follicular phase, which is when the difference was detected. It is not known whether this partial agonist would have caused blunting in the luteal phase also. Two groups have investigated the prolactin response using a different probe, fenfluramine. One study[41] found no differences between symptomatic PMDD women and asymptomatic controls while a second study[42] found blunting in symptomatic women during the luteal phase.

Finally, treatment response is another indicator that 5-HT has a role in the pathophysiology of PMDD. Agents which are specific for the 5-HT transporter are effective treatments for PMDD and include clomipramine,[43,44] fenfluramine,[45] fluoxetine,[28,46-52] paroxetine[53] and sertraline.[54,55].

Importantly there are several studies which suggest that agents working at the 5-HT transporter are more effective than other antidepressants. These include the trial of Ericksson and colleagues[53] which found paroxetine superior to maprotoline and a trial finding greater benefit with fluoxetine than bupropion.[50] Finally a recently presented study found sertraline to be more effective than desipramine.[56]

In sum, literature investigating the psychobiology as well as the treatment of PMDD supports a role for 5-HT in the pathophysiology of the disorder which could therefore provide a potentially useful model for future research.

A Novel Neurotransmitter Balance and Equilibrium Theory of Mental Illness

From these data, we have formulated a neurotransmitter balance theory of mental illness (Fig. 11.2). In this model, three primary neurotransmitters are postulated to mediate specific dimensions of pathophysiology associated with mental illness. Dopamine, noradrenaline and GABA are conceived as mediating thought process, anxiety, and depression, respectively. In a situation of homeostasis and normothymia, the brain maintains a balance among these three neurotransmitters. When, due to stress, environmental disruption, deranged chronobiology, or other poorly understood factors, the neurobiological homeostasis destabilizes and disequilibrates, administration of serotonergic agents is theorized to equilibrate the person's behavioral chemistry back to its natural 'homeostatic set point,' perhaps by re-instituting behavioral inhibition. The advantage of this model is that it attempts to incorporate multiple neurotransmitters and their interactions. The disadvantage, of course, is that it is simplistic and naïve, like all models of the human brain. However, it is via the development and testing of such theoretical models that we will eventually elucidate the mechanism of action of the SSRIs and develop an understanding, at the neuronal and molecular level, of the 5-HT spectrum disorders.

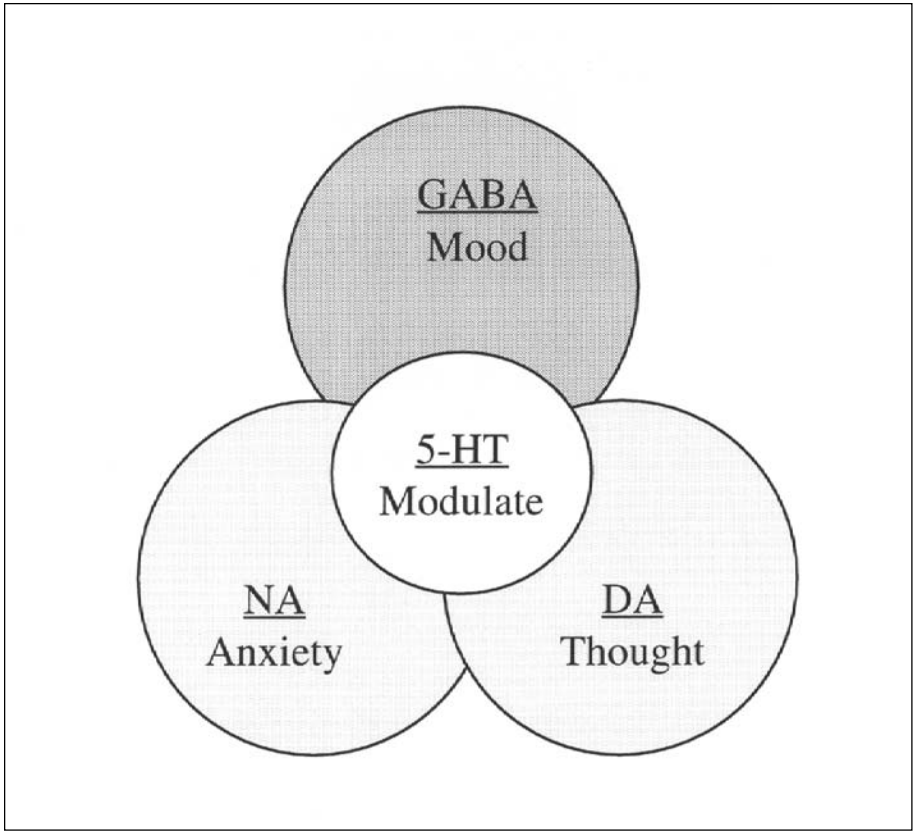

Fig. 11.2. This model conceptualizes anxiety, depression and thought disorder as relating to predominantly noradrenaline (NA), GABA and dopamine (DA), respectively. When the system is destabilized, serotonergic function is also disturbed. 5-HT-selective drugs are theorized to function by returning the system to homeostasis, explaining their clinical utility in a wide variety of disorders.

References

1. Baumgarten HG, Grozdanovic Z. Psychopharmacology of central serotonergic systems. Pharmacopsychiatry 1995; 28:73-79.
2. Stahl SM. Basic psychopharmacology of antidepressants, Part 1: Antidepressants have seven distinct mechanisms of action. J Clin Psychiatry 1998; 59 (suppl 4):5-14.
3. Aghajanian GK. Electrophysiology of serotonin receptor subtypes and signal transduction pathways. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology. New York: Raven Press, 1995: 451-460.
4. Cooper JR, Bloom FE, Roth RH. The Biochemical Basis of Neuropharmacology. Oxford: Oxford University Press, 1996.
5. Petty F, Sherman AD. Regional aspects of the prevention of learned helplessness by desipramine. Life Sci 1980; 26:1447-1452.

6. Petty F, Kramer GL, Wilson L. Prevention of learned helplessness: In vivo correlation with cortical serotonin. Pharmacol Biochem Behav 1992; 43:361-367.
7. Petty F, Sherman AD. Learned helplessness induction decreases in vivo cortical serotonin release. Pharmacol Biochem Behav 1983; 18:649-650.
8. Petty F, Wu J, Kramer GL et al. Serotonin and learned helplessness: A regional study of 5-HT_{1A}, 5-HT_2 receptors and the serotonin transport site in rat brain. J Psychiatr Res 1999; 33:17-22.
9. Pandey FN, Pandey SC, Janicak PG et al. Platelet serotonin-2 receptor binding sites in depression and suicide. Biol Psychiatry 1990; 28:215-222.
10. Sherman AD, Petty F. Neurochemical basis of the action of antidepressants on learned helplessness. Behav Neural Biol 1980; 30:119-134.
11. Martin P, Soubrie P, Puech AJ. Reversal of helpless behavior by serotonin uptake blockers in rats. Psychopharmacology 1990; 101:403-407.
12. Jordan S, Kramer GL, Zukas PK et al. In vivo biogenic amine efflux in medial prefrontal cortex with imipramine, fluoxetine and fluvoxamine. Synapse 1994; 18:294-297.
13. Maser JD, Cloninger CR. Comorbidity of Mood and Anxiety disorders. Washington DC, American Psychiatric Press; 1990.
14. Rush AJ, Cain JW, Raese J et al. Neurobiological bases for psychiatric disorders. In: Rosenberg RN, ed. Comprehensive Neurology. New York: Raven Press, 1991:555-608.
15. Meltzer HY. Role of serotonin in depression. In: Whitaker-Azimitia PM, Peroutka S, eds. The Neuropharmacology of Serotonin. Ann NY Acad Sci USA 1990: 486-500.
16. Meltzer HY, Lowy MT. The serotonin hypothesis of depression. In: Meltzer HY, ed. Psychopharmacology: The Third Generation of Progress. New York: Raven Press, 1987:513-526.
17. Lopez-Ibor JJ Jr. The involvement of serotonin in psychiatric disorders and behaviour. Br J Psychiatry 1988; 153(suppl 3):26-39.
18. Delgado PL, Charney DS, Prince LH et al. Neuroendocrine and behavioral effects of dietary tryptophan restriction in healthy subjects. Life Sci 1989; 45:2323-2332.
19. Delgado PL, Charney DS, Price LH et al. Serotonin function and the mechanism of antidepressant action. Arch Gen Psychiatry 1990; 47:411-418.
20. Delgado PL, Prince LH, Miller BL et al. Rapid serotonin depletion as a provocative challenge test for patients with major depression: Relevance to antidepressant action and the neurobiology of depression. Psychopharmacol Bull 1991; 27:321-330.
21. Maes M, Meltzer HY (1995). The serotonin hypothesis of major depression. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York: Raven Press, 1995:933-944.
22. Mayberg HS, Robinson RG, Wong DF et al. PET imaging of cortical S2-serotonin receptors after stroke: Lateralized changes and relationship to depression. Am J Psychiatry 1988; 145:937-943.
23. D'Haenen H, Bossuyt A, Mertens J et al. SPECT imaging of serotonin(2) receptors in depression. Psychiat Red Neuroimaging 1992; 45:227-237.
24. Grasby PM, Sharp T, Allen T et al. Effects of the 5-HT_{lA} partial agonists gepirone, ipsapirone and buspirone on local cerebral glucose utilization in the conscious rat. Psychopharmacology 1992; 106:97-101.
25. Mann JJ, Malone KM, Diehl DJ et al. Demonstration in vivo of reduced serotonin responsibility in the brain of untreated depressed patients. Am J Psychiatry 1996; 153:174-182.
26. Mann JJ, Malone KM, Diehl DJ et al. Positron emission tomographic imaging of serotonin activation effects on prefrontal cortex in healthy volunteers. J Cereb Blood Flow Metab 1996; 16:418-426.
27. Kapur S, Meyer J, Wilson AA et al. Modulation of cortical neuronal activity by a serotonergic agent: A PET study in humans. Brain Res 1994; 646:292-294.
28. Yonkers KA, Halbriech U, Freeman E et al. The Sertraline Premenstrual Dysphoric Collaborative Study Group. Symptomatic improvement of premenstrual dysphoric disorder with sertraline treatment. JAMA 1997; 278:983-938.

29. Graze KK, Nee J, Endicott J. Premenstrual depression predicts future major depressive disorder. Acta Psychiatr Scand 1990; 81:201-205.
30. Halbreich U, Tworek H. Altered serotonergic activity in women with dysphoric premenstrual syndromes. Int J Psychiatry Med 1993;23:1-27.
31. Ashby CRJ, Carr LA, Cook CL et al. Alteration of platelet serotonergic mechanisms and monoamine oxidase activity in premenstrual syndrome. Biol Psychiatry 1988; 24:225-233.
32. Taylor DL, Mathew RJ, Weinman ML. Serotonin levels and platelet uptake during premenstrual tension. Neuropsychobiology 1984; 12:16-18.
33. Malmgren R, Collins A, Nilsson C-G. Platelet serotonin uptake and effects of vitamin B6-treatment in premenstrual tension. Neuropsychobiology 1987; 18:83.
34. Rojansky N, Halbreich U, Zander K et al. Imipramine receptor binding and serotonin uptake in platelets of women with premenstrual changes. Gynecol Obstet Invest 1991; 31:146-152.
35. Steege JF, Stout AL, Knight BS et al. Reduced platelet tritium-labeled imipramine binding sites in women with premenstrual syndrome. Am J Obstet Gynecol 1992; 167:168-172.
36. Rapkin AJ. The role of serotonin in premenstrual syndrome. Clin Obstet 1992; 35:629-636
37. Menkes DB, Coates DC, Fawcett JP. Acute tryptophan depletion aggravates premenstrual syndrome. J Affect Disord 1994; 32:37-44.
38. Heath AC, Yonkers KA, Orsulak P et al. Tryptophan depletion in premenstrual dysphoric disorder. Biol Psychiatry 1998; 43:1:54S.
39. Bancroft J, Cook A, Davidson D et al. Blunting of neuroendocrine responses to infusion of L-tryptophan in women with perimenstrual mood change. Psychol Med 1991; 21:305-312.
40. Yatham LN. Is 5HT-1A receptor subsensitivity a trait marker for late luteal phase dysphoric disorder? A pilot study. Can J Psychiatry 1993; 38:662-664.
41. Bancroft J, Cook A. The neuroendocrine response to *d*-fenfluramine in women with premenstrual depression. J Affect Disord 1995; 36:57-64.
42. Fitzgerald M, Malone K, Harrison W et al. Blunted serotonin response to fenfluramine challenge in premenstrual dysphoric disorder. Am J Psychiatry 1996; 154:556-558.
43. Sundblad C, Modigh K, Andersch B et al. Clomipramine effectively reduces premenstrual irritability and dysphoria: a placebo-controlled trial. Acta Psychiatr Scand 1992; 85:39-47.
44. Sundblad C, Hedberg MA, Eriksson E. Clomipramine administered during the luteal phase reduces the symptoms of premenstrual syndrome: A placebo-controlled trial. Neuropsychopharmacology 1993; 9:133-145.
45. Brzezinski AA, Wurtman JJ, Wurtman RJ et al. *d*-fenfluramine suppresses the increased calorie and carbohydrate intakes and improves the mood of women with premenstrual depression. Obstet Gynecol 1990; 76:296-300.
46. Stone AB, Pearlstein TB, Brown WA. Fluoxetine in the treatment of late luteal phase dysphoric disorder. J Clin Psychiatry 1991; 52:290-293.
47. Wood SH, Mortola JF, Chan Yuen-F et al. Treatment of premenstrual syndrome with fluoxetine: A double-blind, placebo-controlled, crossover study. Obstet Gynecol 1992; 80:339-344.
48. Menkes DB, Taghavi E, Mason PA et al. Fluoxetine treatment of severe premenstrual syndrome. Br Med J 1992; 305:346-347.
49. Steiner M, Steinberg S, Stewart D et al. Fluoxetine in the treatment of premenstrual dysphoria. N Engl J Med 1995; 332:1529-1534.
50. Pearlstein TB, Stone AB, Lund SA et al. Comparison of fluoxetine, bupropion, and placebo in the treatment of premenstrual dysphoric disorder. J Clin Psychopharmacol 1997; 17:261-265.
51. Ozeren S, Corakci A, Yucesoy I et al. Fluoxetine in the treatment of premenstrual syndrome. Eur J Obstet Gynecol Reprod Biol 1997; 73:167-170.
52. Su T-P, Schmidt PJ, Danaceau MA et al. Fluoxetine in the treatment of premenstrual dysphoria. Neuropsychopharmacology 1997; 16:346-356.
53. Eriksson E, Hedberg MA, Andersch B et al. The serotonin reuptake inhibitor paroxetine is superior to the noradrenaline reuptake inhibitor maprotiline in the treatment of premenstrual syndrome. Neuropsychopharmacology 1995; 12:169-176.

54. Yonkers KA, Halbreich U, Freeman EW et al. Sertraline in the treatment of premenstrual dysphoric disorder. Psychopharmacol Bull 1996; 32:41-46.
55. Young SA, Hurt PH, Benedek DM et al. Treatment of premenstrual dysphoric disorder with sertraline during the luteal phase: A randomized, double-blind, placebo-controlled crossover trial. J Clin Psychiatry 1998; 59:76-80.
56. Freeman EW, Rickels K, Sondheimer SJ. Sertraline versus desipramine in PMS treatment. Symposia No 118C, presented at the American Psychiatric Association Annual Meeting, May 30-June 4, 1998: Toronto, Ontario, Canada.

Chapter 12

SSRIs: Where Now, Where Next?

David J. Heal and Sharon C. Cheetham

It is interesting to note that in the title of their review on fluoxetine ('Prozac', Lilly), Wong, Bymaster and Engleman[1] describe this drug as "the first selective serotonin reuptake inhibitor." Like much of the subject, this claim owes rather more to perpetuating public perception than to reality. In fact, the first selective serotonin reuptake inhibitor (SSRI) to enter the market as an antidepressant drug was zimelidine ('Zelmid', Astra) which was launched in the UK and Sweden in 1982. Zimelidine was subsequently withdrawn for producing severe idiosyncratic toxicity in some patients. In Europe, the introduction of zimelidine was followed by another SSRI, fluvoxamine ('Favarin', Solvay-Duphar) which was launched as an antidepressant in Switzerland in 1983; however, this drug was not launched in the USA until 1994 and then it was for the treatment of obsessive-compulsive disorder, not depression. It was only in 1988 that fluoxetine appeared on the market in the USA as a novel antidepressant, thus making it the third, not the first, SSRI.

On the basis of the relatively modest sales of zimelidine and fluvoxamine, no-one would have predicted the manner in which fluoxetine's introduction in the USA would so dramatically expand the antidepressant market, and in the process, enter the folklore and culture of a generation, rather like the barbiturates in the 1950s and the benzodiazepines in the 1960s and 1970s. Analogous to these earlier phenomena, the success of fluoxetine probably owes as much to circumstance as to the combination of its improved qualities as an antidepressant and Lilly's extremely astute marketing of the product. In this chapter, we will attempt to evaluate the impact that fluoxetine and other SSRIs have had on the antidepressant market and the value of their contribution towards the goal of the 'ideal' antidepressant. Finally, we will discuss the status of research and development in the field of SSRIs and where the opportunities lie for the next generation of antidepressant drugs.

Analysis of the Impact of the SSRIs on the Antidepressants Market

The generic and trade names of the SSRIs which have received regulatory approval are given in Table 12.1, along with the indications for which they have been approved. Their chemical structures are shown in Figure 12.1.

It is clearly evident from the data presented in Figure 12.2 that the antidepressants market has grown and continues to grow at a very substantial rate. In fact, between 1990 and 1997 total world sales of antidepressants increased by an average of 34% year on year, and in 1992, sales increased by a staggering 67%. Based on 1997 figures, the current value of worldwide sales of antidepressants is estimated to be £(sterling)3.5 billion. It is also apparent from these figures that the USA accounts for ~70% of total worldwide antidepressant sales and it has been the major contributor to growth in this sector. The reasons for this market expansion are three-fold. The first is the cost of the SSRIs relative to the tricyclics. The latter were introduced as antidepressants predominantly in the 1950s and '60s and by the time of

Selective Serotonin Reuptake Inhibitors (SSRIs): Past, Present and Future,
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Table 12.1. Status of SSRIs

Generic name	Company	Trade names	Approved indication
Zimelidine	Astra	Zelmid	Depression (withdrawn)
Fluoxetine	Lilly	Prozac Digassin Fluctin Fluctine Fontex Ladose Lovan Portal Prozyn Saurat	Depression Obsessive-compulsive disorder Bulimia Anxiety[1]
Sertraline	Pfizer	Lustral Zoloft Altruline Tatig Gladem	Depression Obsessive-compulsive disorder
Paroxetine	Smith Kline-Beecham -licensed from Ferrosan	Seroxat Paxil Aropax Tagonis Frosinor Deroxat Sereupin Motivan	Depression Obsessive-compulsive disorder Panic disorder
Citalopram	Lundbeck	Cipramil Seropram Cipram Elopram Celaxa	Depression
Fluvoxamine	Solvay-Duphar	Fevarin Faverin Floxyfral Luvox Dumyrox Dumirox Flavoxyl	Depression[2] Obsessive-compulsive disorder

[1], not approved in any major territory
[2], not approved for the treatment of depression in the USA.

the launch of the SSRIs, many no longer had patent protection and were already available as low cost generics. As a market dominated by old products, many of which were being squeezed by generic competition, there was ample opportunity for a major increase in its value. However to achieve success, the SSRIs had to be recognized by psychiatrists and general practitioners as a major step forward in antidepressant therapy. At the time of the introduction of the SSRIs in the late 1980s, there was not the same degree of downward pressure on drug costs which there is today and, in addition, drug costs comprise a relatively small proportion of total treatment charges in the USA. Nevertheless, the cost per month of prescribing an SSRI was 10- to 15-fold greater than that of prescribing a low cost or generic tricyclic antidepressant and, for this change to occur, physicians had to be convinced of the increased benefit of SSRI treatment. Led very much from the front by Lilly, the SSRIs were marketed as an effective, safer and better tolerated alternative to the tricyclic antidepressants. The

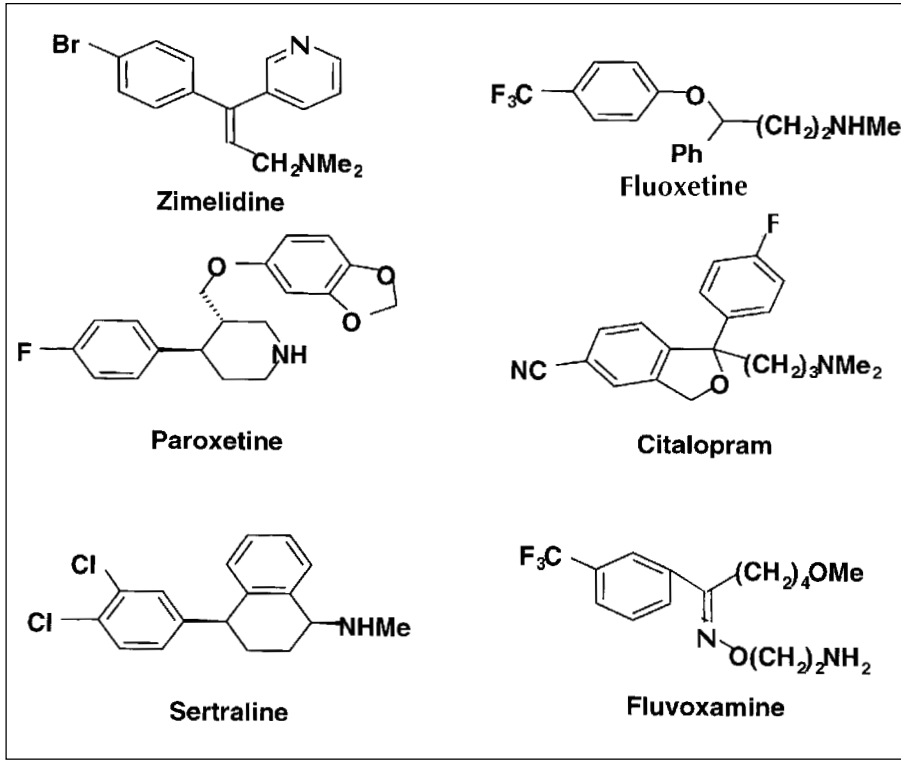

Fig.12.1 Structures of the SSRIs which have reached the marketplace.

validity of these claims is examined in detail later in this chapter. To Lilly's credit, this proved to be an immensely persuasive campaign and its impact on the prescribing of antidepressants, as shown by sales of different classes of antidepressant from 1986 (prior to the introduction of fluoxetine in 1988) to 1997 is shown in Figure 12.3. As these pie-charts show, the tricyclics have effectively been ousted in just a decade from a position of supremacy in the antidepressant market to one of apparently minor importance. However, due to the cost differential between the SSRIs and the tricyclics (and other older antidepressant drugs), the dominance by the former is somewhat overemphasized when judged by cash values. Thus, if one compares sales by the number of prescriptions issued, it is evident that in 1997 the tricyclics still comprise ~20% of antidepressant prescriptions in the USA; this compares with a figure of ~5% if one looks at sales by cash value (Fig. 12.4).

In this section, we have deliberately focused on the USA market, because it is here that the revolution in antidepressant prescribing occurred. In fact, zimelidine and fluvoxamine had been launched into the European market several years before fluoxetine was introduced in the USA. However, neither Astra (zimelidine), nor Solvay-Duphar (fluvoxamine) positioned their SSRIs as being a complete innovation in antidepressant therapy (probably a more realistic position when one critically examines their performance with respect to the tricyclics; see later in the chapter). The consequence of this more conservative strategy was that these SSRIs failed to loosen the stranglehold which the tricyclics had on the European antidepressants market. In fairness, it must be stated that zimelidine enjoyed only a brief period on the market before being withdrawn for inducing Guillain-Barré syndrome in

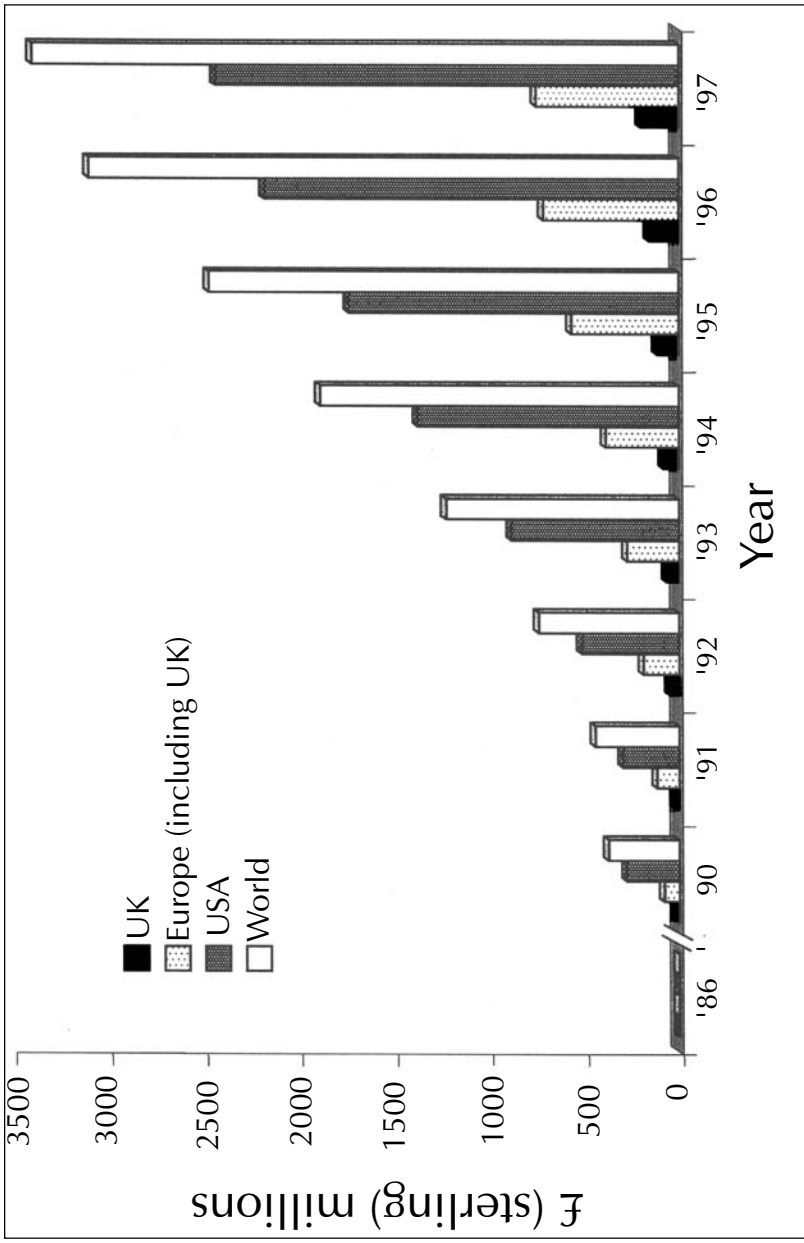

Fig.12.2. Worldwide—growth in the value of the antidepressant market (Data taken from IMS World Review).

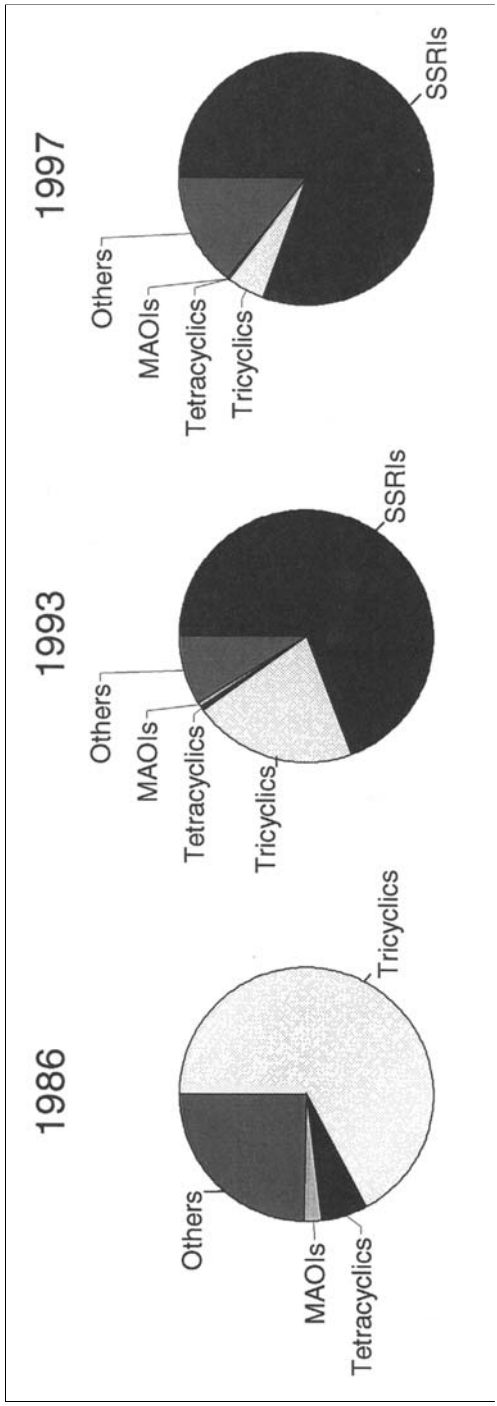

Fig. 12.3. USA—SSRIs as a proportion of total sales of antidepressants (Data taken from IMS World Review.

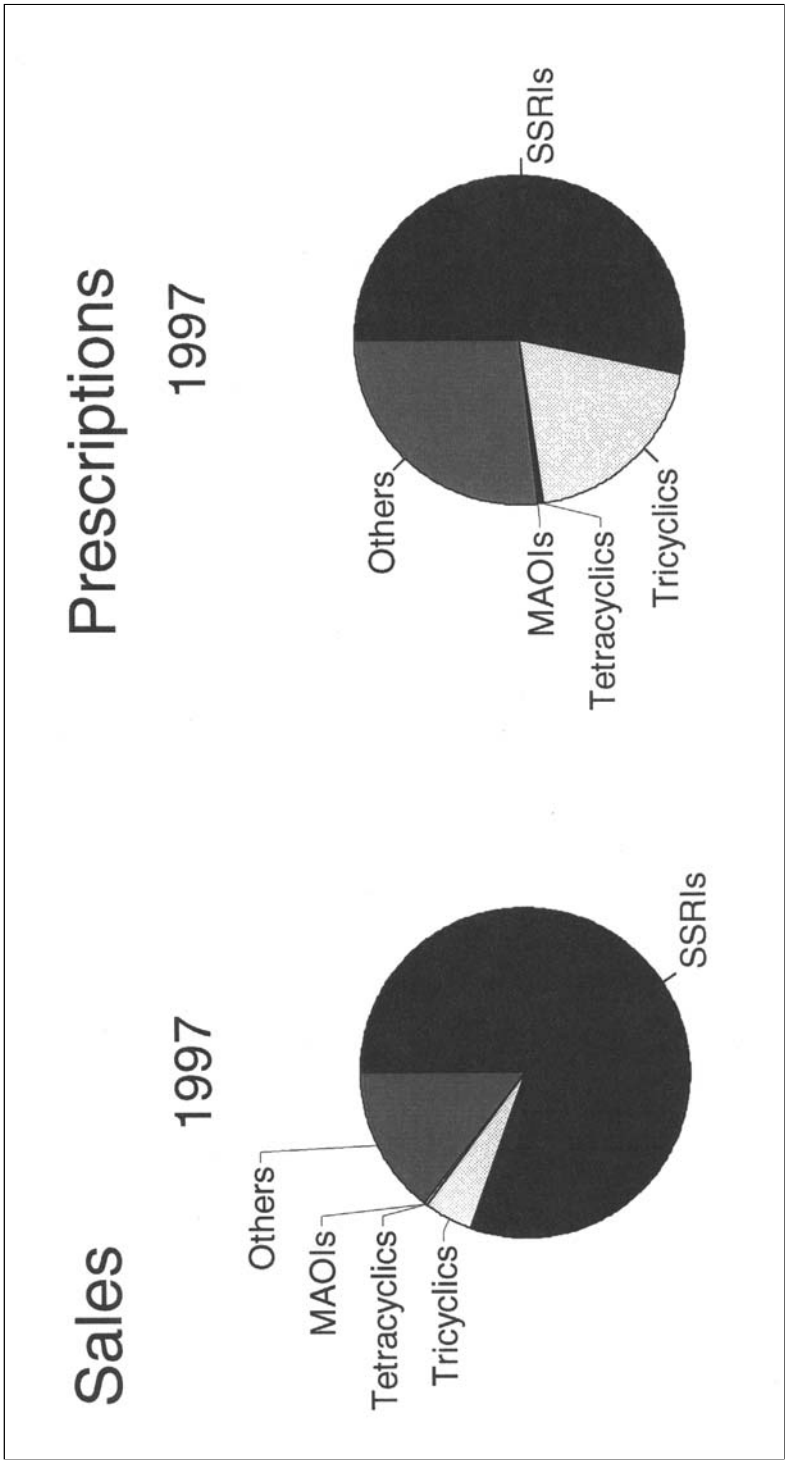

Fig. 12.4. USA—A comparison of SSRIs as a proportion of 1997 antidepresant sales and prescriptions (Data taken from IMS World Review).

some patients, and Solvay-Duphar lacked the marketing muscle required to manage a sea-change in antidepressant prescribing habits. Inevitably, events in the USA and the 'hype' surrounding the success of fluoxetine led to a re-evaluation of antidepressant therapy in other territories; a change which received the maximum impetus which could be provided by a major pharmaceutical company, like Lilly. This process was further facilitated by the considerable efforts of both Pfizer (sertraline) and SmithKline-Beecham (paroxetine) which also entered the antidepressants market. As shown by the total sales of various classes of antidepressants worldwide (Fig. 12.5), the final outcome has been almost identical to that which occurred in the USA; the only difference being that the takeover by the SSRIs of the antidepressants market in the rest of the world lagged by 2-3 years behind the USA (see Figs. 12.3 and 12.5).

The second strategy adopted by the pharmaceutical industry was to initiate an educational campaign to increase awareness of depression and to emphasize that many patients with depression suffer needlessly because this disorder goes unrecognized. It is evident from the growth in the number of prescriptions for antidepressants issued per year in the USA (Fig. 12.5) that this has been a very successful marketing exercise. Critics have argued that, rather than raising awareness of depression as a serious psychiatric disorder, this approach has trivialized the condition reducing it merely to the level of a lifestyle issue. There is little doubt that the SSRIs are viewed by many as pharmaceutical accessories for survival in the stressed-out '90s. A process which has not been helped by some extravagant claims of positive personality changes in patients receiving SSRI treatment.

The third strategy has been to explore every possible indication where there is evidence (either scientific or empirical) to suggest that the SSRIs may be of therapeutic value. This has led to the registration of various SSRIs for obsessive-compulsive disorder, bulimia, panic disorder and social phobia, in addition to depression. It has also led to clinical trials in other conditions, e.g., obesity, where success has not been forthcoming. However overall, there have been more winners than losers and when off-label prescribing for a host of other psychiatric and non-psychiatric disorders is added in, it has had a major impact in the sale of the SSRIs (this strategy is reviewed later in the chapter).

When the sales of individual SSRIs are examined, it is evident that fluoxetine, as the first of its class to be marketed in the USA, dominated sales in the early years. However as shown in Fig. 12.7, the entry of other major pharmaceutical industry players, i.e., Pfizer with sertraline and SmithKline-Beecham with paroxetine, has provided a strong challenge to Lilly's leadership with fluoxetine.

The major problem for the pharmaceutical industry, and Lilly in particular, is how to deal with the loss of patent cover on fluoxetine in 2000 in Europe and 2001 in the USA. In the latter market, genericization almost immediately erodes prices by ~90%. This occurrence will not only undermine Lilly's branded fluoxetine (Prozac), it will also provide a remarkably cheap alternative to the other patent protected SSRIs, and as such, it will have a major negative impact on the SSRI market in general.

It is this prospect which is driving antidepressant research in the pharmaceutical industry. Having gratefully accepted the plaudit that the SSRIs are 'wonder drugs' (and they have sold accordingly!), it is now very difficult for the major pharmaceutical companies to stand the world on its head by saying that the SSRIs were not so good after all. The problem here is that to gain widespread acceptance for the next generation of antidepressant drugs, the pharmaceutical companies will have to demonstrate unequivocally to the regulatory authorities, the prescribers and even the patients, that these new drugs are better than the SSRIs. Efficacy and rapidity of therapeutic efficacy with respect to the SSRIs are the challenges which the pharmaceutical companies have generally accepted as being those most likely to

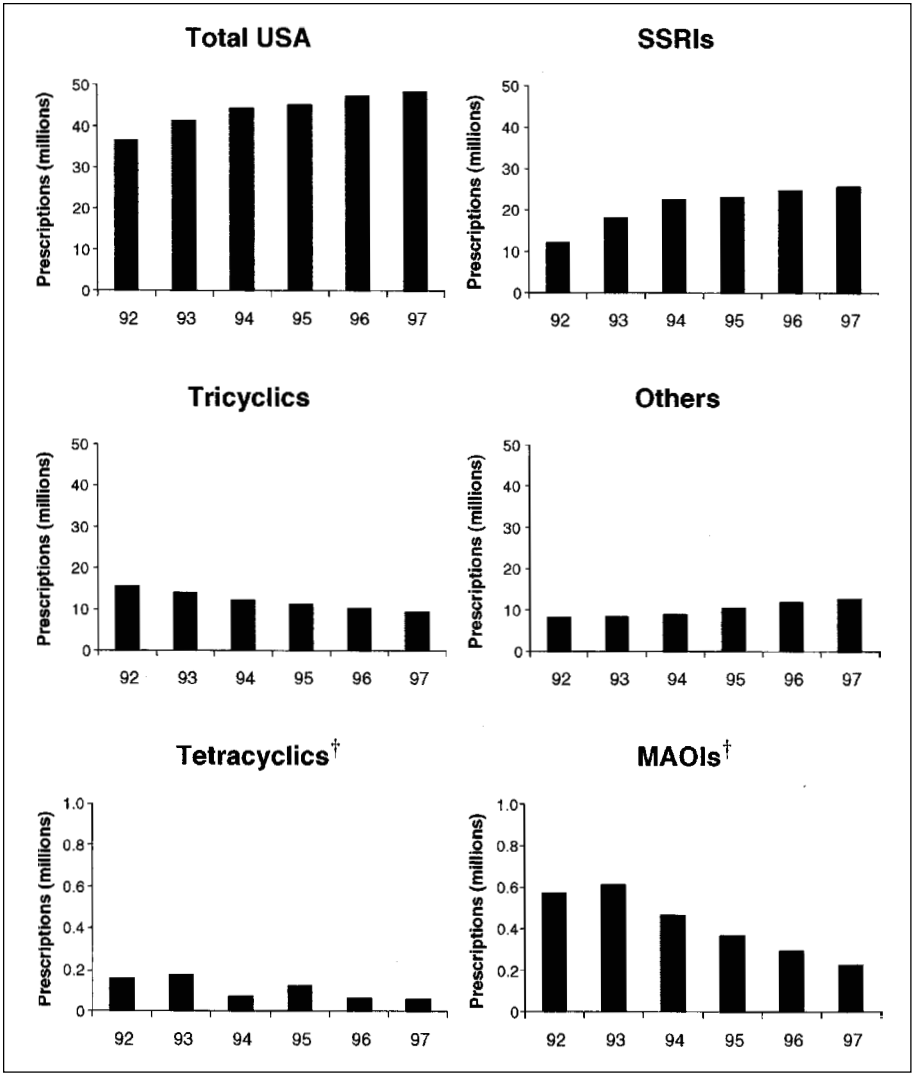

Fig. 12.5. USA—growth in the number of antidepressant prescriptions (Data taken from IMS World Review) † Note scale change.

lead to success. Later in this chapter, we will discuss the scientific strategies to achieve these objectives and also the likelihood that this will lead to therapeutic and commercial success.

An Evaluation of the SSRIs Against the Criteria for the 'Ideal' Antidepressant Drug

In order to assess objectively the contribution which the SSRIs have made to the field of antidepressant therapy, it is appropriate to consider the postulated role of the monoamines in the etiology of depression and the pharmacological rationale which underpinned the

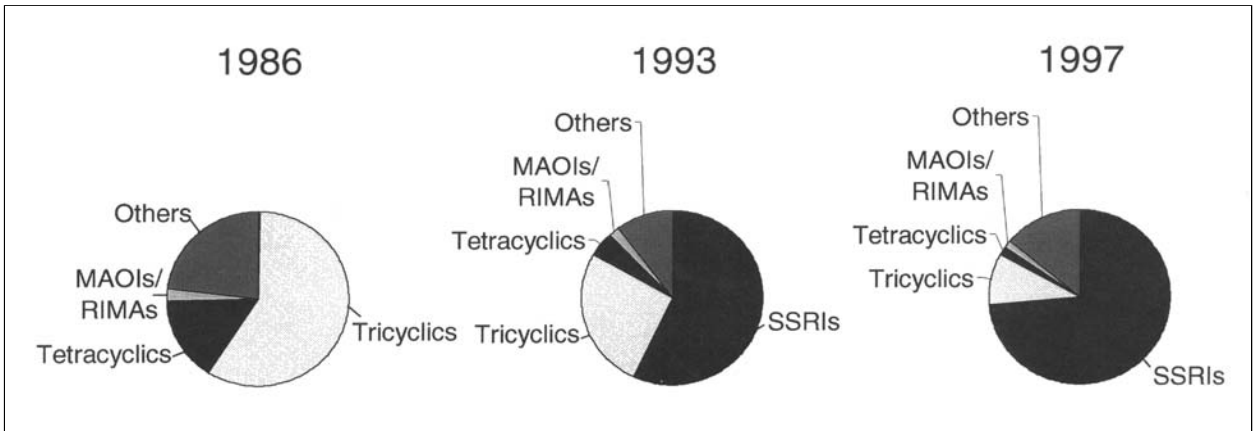

Fig. 12.6. Worldwide—SSRIs as a proportion of total sales of antidepressants (Data taken from IMS World Review).

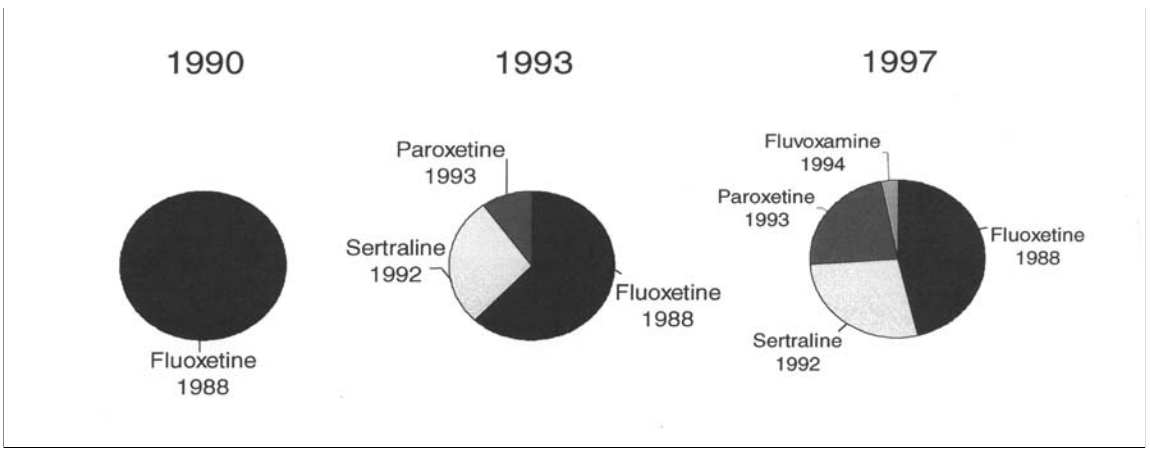

Fig. 12.7. Worldwide—sales of individual SSRIs as a proportion of total sales of SSRIs (Data taken from IMS World Review).

development of the SSRIs. Reserpine (which depletes central monoamine stores) was found to produce symptoms of depression in patients treated for hypertension. Conversely, iproniazid (later found to be an irreversible monoamine oxidase inhibitor[2]) was found to have mood-elevating properties and to produce euphoria when used to treat patients with tuberculosis[3] and imipramine (later found to be a monoamine reuptake inhibitor),[4,5] although initially developed as an antipsychotic, was found to be an effective antidepressant agent.[6] Together, these observations formed the basis of the 'monoamine hypothesis of depression' which states that depression results from reduced monoaminergic drive in the CNS and antidepressants work by correcting the dysfunction. However, it is important to note that the originators of this hypothesis could be divided into two camps, i.e., those who believed that depression resulted from a brain deficit of noradrenaline[7,8] and those who believed it was due to a deficit in 5-hydroxytryptamine (5-HT).[9-11]

The 'first generation' of antidepressants consisted of the non-selective, irreversible monoamine oxidase inhibitors (MAOIs) and the tricyclic monoamine reuptake inhibitors. Since the former inhibit the catabolism of all central monoamines equally, i.e., noradrenaline, 5-HT and dopamine, whilst the latter (the so-called 'tricyclic antidepressants;' TCAs) include drugs which do not discriminate between noradrenaline and 5-HT, and those which act preferentially on one or other of these monoamines (see: Table 12.2), there was no evidence to indicate which of these two monoamines had the greater relevance to depression and its treatment.

As shown in Table 12.2, the SSRIs are potent 5-HT reuptake inhibitors in vitro with either good or excellent separation versus their K_i values for the inhibition of noradrenaline reuptake. It is also apparent that several TCAs exhibit significant in vitro affinity for the 5-HT reuptake site and, clomipramine in particular, shows ~5-fold selectivity as a 5-HT reuptake inhibitor. However, it is also important to point out that the secondary amine metabolites of many tricyclic antidepressants, e.g., desipramine, nortriptyline, are highly selective inhibitors of noradrenaline reuptake (Table 12.2).

As shown in Table 12.3, antidepressant drugs can be evaluated against five major criteria. In terms of efficacy, the 'ideal' antidepressant would effectively treat mild and severe depression of all types and alleviate depression completely (not merely reduce the Hamilton rating scale for depression (HAM-D) by 50% or achieve a rating of 'much improved' on the Clinical Global Impressions scale; criteria often employed to assess antidepressant efficacy in clinical trials).[12] The onset of clinical improvement would be concurrent with the initiation of treatment. The 'ideal' antidepressant would produce minimal side-effects and it would also be safe when taken in overdose. Finally, cessation of treatment would not be accompanied by any syndrome of physical or psychological withdrawal.

The irreversible monoamineoxidase (MAO) inhibitors fairly rapidly fell into disfavor as antidepressants (for reviews see refs. 13-15) and it was the tricyclic monoamine reuptake inhibitors which provided the virtually unchallenged mainstay of antidepressant therapy for almost 25 years prior to the introduction of the SSRIs. In terms of efficacy, the 'first generation' tricyclic antidepressants have been clearly demonstrated to produce clinically significant improvements in depressed patients and to be statistically superior to placebo.[16] However, it is also well accepted that only 65-70% of patients respond to tricyclic therapy and, furthermore, even in responders efficacy is often incomplete.[17-20]

The SSRIs have been similarly shown to be demonstrably more effective than placebo in double-blind clinical trials of major depression.[21-26] However, analysis of these data and those taken from various meta-analyses of clinical trials comparing the SSRIs with tricyclics (for a review see ref. 27) indicates a significant dropout rate of ~7% for lack of efficacy, and even where efficacy is observed, the magnitude of this effect is generally only 20–35% better than that observed with placebo (see also: Chapter 3). Clinical trials comparing the efficacy

in major depression of individual SSRIs versus individual TCAs[21,23-26,28-31] or meta-analyses which generally compare these two classes of antidepressant (for a review see ref. 27) clearly demonstrate that the SSRIs are no more effective than the tricyclics. Studies directly comparing the efficacy of different SSRIs one with another in clinical trials of depression are not numerous. Often, they are relatively small trials of limited duration and, as a consequence, not ideal for detecting differences between treatments. However with that limitation in view, there is no compelling evidence to indicate any difference between the efficacy of individual SSRIs.[32-37] As a confirmation of this perspective, Zarate et al[38] reported that depressed patients who failed to respond to fluoxetine treatment, due either to lack of efficacy or adverse events, fared little better when transferred to sertraline.

In terms of rapidity of therapeutic effect, there is more variability between clinical studies. However when viewed overall, there is no evidence to suggest that the SSRIs are faster-acting antidepressants than the tricyclics, i.e., it is accepted that major clinical improvement occurs only after 2–3 weeks of treatment.

Since there is ample clinical evidence to demonstrate that the SSRIs are neither more efficacious nor more rapidly acting antidepressants than the tricyclics, the pharmaceutical industry's marketing effort for the SSRIs has been focused on tolerability and safety rather than efficacy. Almost all of the tricyclics have relatively high affinity for α_1-adrenergic, histamine H_1 and muscarinic cholinergic receptors (Table 12.4;[39-42]).

The α_1-adrenoceptor antagonist action of the tricyclics produces postural (orthostatic) hypotension; this occurs in as many as 20% of patients.[43] This side-effect can exacerbate symptoms of pre-existing cardiovascular dysfunction, and it has been potentially implicated in an increased risk of falls and physical injury in elderly patients. α_1-Adrenoceptor antagonism may also aggravate narrow angle-glaucoma. Blockade of muscarinic cholinergic receptors by tricyclics produces the common side-effects of dry mouth, blurred vision, constipation and urinary retention. Cholinergic inhibition can also induce sinus tachycardia and may even produce some short-term memory loss.[43] The antihistaminergic actions contribute to symptoms of sedation, drowsiness and weight gain (which is observed with some, but not all, tricyclic antidepressants). It is generally thought that it is the combination of anticholinergic activity, monoamine reuptake inhibition and direct depressant actions, which can evoke mild tachycardia in some patients. Of rather more significance, these pharmacological effects can provoke abnormalities in cardiac conduction, which include prolongation of PR, QRS or QT intervals and flattening or inversion of T-waves due to slowing of both atrial and ventricular depolarization. This slowing of depolarization can result in atrio-ventricular, bundle branch block or premature ventricular contractions.

The SSRIs lack affinity for α_1-adrenergic, muscarinic and histaminergic receptors[41,44,45] and, as a consequence, do not induce anticholinergic, cardiovascular or sedative side-effects.[23,25,27,46,47] In their place, however, reside an equally impressive array of side-effects which derive specifically from the serotonergic mode of action of the SSRIs. One major drawback of the SSRIs is their propensity to cause a high incidence (15–35%) of nausea and gastrointestinal disturbance, mainly vomiting and diarrhea.[23,25] The incidence of these side-effects is significantly worse than in patients receiving tricyclic therapy,[48-51] although it is claimed that they lessen with continued SSRI treatment.[23,25] Other side-effects frequently reported with the SSRIs include sedation, dizziness, agitation, fatigue and tremor.[23,25,46,47] Sexual dysfunction is also a major problem with SSRI treatment (see also: Chapter 6). It mainly consists of delayed ejaculation or anorgasmia, but it can include erectile dysfunction. Although the SSRIs are purported to reduce libido in both men and women,[23,25,46,52-54] it is generally accepted that treatment with SSRIs constitutes a greater problem for sexual functioning in men. Estimates of the incidence of sexual dysfunction vary from between 8-20% of patients,[23,46] but it is also accepted that under-reporting is likely.[25,46] In some

Table 12.2. Potency of various 'first and second generation' antidepressants as inhibitors of monoamine reuptake

	K_i values (nM)		Selectivity ratio
Antidepressants	**5-HT**	**NA**	**5-HT: NA[c]**
'First Generation'			
Desipramine[a]	340	1	0.003
Nortriptyline[a]	260	4	0.015
Doxepin[a]	280	19	0.07
Imipramine[a]	42	13	0.31
Dothiepin[a]	110	34	0.31
Amitriptyline[a]	66	24	0.36
Clomipramine[a]	5.4	28	5.2
'Second Generation'			
Fluoxetine[a]	12	280	23
Paroxetine[b]	1	33	33
Zimelidine[a]	72	3200	44
Fluvoxamine[a]	7	500	71
Sertraline[b]	3	220	73
Citalopram[a]	1	4000	4000

Data are taken from [a], Richelson and Pfenning[160] or [b], Bolden-Watson and Richelson.[161]
[c], The larger the number the more selective the drug in blocking the reuptake of 5-HT.

studies, the incidence has been reported to be as high as 75%, with 25% of those affected discontinuing medication for this reason and a further 50% reducing their dose to alleviate the discomfort.[23] In a recent systematic study of this problem, Modell et al[54] compared the effect on male and female sexual function of bupropion ('Wellbutrin', Burroughs-Wellcome; a weak, selective dopamine reuptake inhibitor antidepressant) with those of various SSRIs, i.e., fluoxetine, paroxetine and sertraline. These investigators reported a similar effect of each of the SSRIs with approximately 70% of patients experiencing adverse sexual side-effects, i.e., loss of libido, arousal and negative impact on orgasm. In contrast,

Table 12.3. Criteria for assessing the 'ideal' antidepressant drug

1. Efficacy
2. Onset of clinical effect
3. Side-effect profile
4. Toxicity in overdose
5. Withdrawal effects

77% of patients on bupropion reported positive effects of this antidepressant on sexual function.[54] Overall, therefore, it appears that this is a negative aspect of SSRI treatment which is only now beginning to be fully appreciated. On this basis, it is clear that whilst the SSRIs do not evoke anticholinergic, sedative and cardiovascular side-effects associated with the tricyclic antidepressants, they bring with them their own basket of problems, some of them serious. It is, therefore, not surprising to discover that, in clinical trials, dropouts due to side-effects are 7-23% (median 15%) for patients taking SSRIs compared with 7-44% (median 21%) for patients on tricyclics.[55] Thus, although there is some improvement in compliance with patients on SSRIs versus tricyclics, it is fairly modest (approximately 6%). This view is supported by a number of meta-analyses which have compared the dropout rates of patients on SSRIs and tricyclics. In the most recent study, Anderson and Tomenson[56] reported a small, but significant, difference in favor of the SSRIs in terms of dropouts due to adverse events (SSRIs=14.4% versus tricyclics=18.8%), but no difference in either the dropout rate for lack of efficacy, or importantly, overall dropout rate.

The SSRIs have little effect on cardiac function[1,23,46] and are consequently suggested to be more suitable for treating elderly patients (see also: Chapter 4). This relatively benign cardiovascular profile has also contributed to the perception that the SSRIs are much safer than the tricyclic antidepressants when taken in overdose. This is because when tricyclics are taken in large quantities the cardiotoxic sequelae, respiratory depression and coma can prove fatal. Death from tricyclic overdose is primarily due to cardiac arrest.[57] This issue has provoked considerable criticism of the tricyclics.[58-60] Since it has been estimated that 15% of patients with major depression will die from suicide,[61] which is about 30 times greater than for the general population, on the face of it, this information should provide ample evidence to support the use of SSRIs rather than tricyclics in the treatment of depression (see also: Chapter 7). It is certainly an argument which has been very effectively employed in the marketing of the SSRIs; it is also an argument which has sparked off a great deal of controversy. Whilst there are clinicians who unequivocally support the use of the SSRIs on the basis of this very important safety issue,[62,63] there are others who believe that the case for the SSRIs is not so compelling.[27,64-66] The counter-argument is that although the tricyclics are undoubtedly highly toxic when taken in overdose, most patients under primary-care physicians are only mildly to moderately depressed. Consequently, they are at little risk of committing suicide. For those who do commit suicide, TCAs, taken either alone or in combination with other substances, only account for approximately 6% of successful attempts. Furthermore, there is evidence which suggests that the overall rate of suicide in, for example England and Wales, has remained relatively constant between 1975 and 1992[27] and suicide victims taking safer antidepressants resort to other, often more violent, methods

Table 12.4. Affinity of various tricyclic antidepressants for α_1-adrenoceptors, histamine H_1 and muscarinic receptors in human brain frontal cortex

	K_i values (nM)		
	α_1	H_1	muscarinic
Desipramine	130	110	198
Nortriptyline	60	10	150
Doxepin	24	0.24	80
Imipramine	90	11	90
Dothiepin	470	3.6	25
Amitriptyline	27	1.1	18
Clomipramine	38	31	37

Data are taken from Richelson and Nelson.[41]

to achieve their goal.[64] Another complicating factor was a report in 1990 which suggested that 6 patients receiving fluoxetine developed intense suicidal ideation[67] and this and subsequent studies suggested that this manifestation may be linked to the occurrence of akathisia and agitation.[67-70] Whilst meta-analyses have been conducted which demonstrate that fluoxetine reduces suicidal ideation,[71,72] it has also been pointed out that these trials were not designed to detect emergent suicidal ideation and, furthermore, that Item 3 of the HAM-D is an insensitive measure for detecting suicidal ideation.[73] When these two pieces of evidence are considered together, it is apparent that whilst safety in overdose played a key role in the marketing of the SSRIs and it has undoubtedly been a major factor in establishing their sector dominance, when rigorously examined this argument is far from flawless.

Drug dependence is not a serious problem with either the SSRIs or the tricyclics (see also: Chapter 5). With both types of antidepressant, abrupt cessation of treatment can lead to a syndrome of nausea, vomiting, cramps and general malaise.[19,20,46,74-77] It has been suggested for the tricyclics[78,79] and paroxetine[80] that withdrawal effects may be due to rebound cholinergic actions, but this hypothesis fails to explain why other SSRIs, which lack anticholinergic effects, also produce identical withdrawal syndromes. It is, however, generally accepted that gradual tapering of TCA or SSRI treatment generally circumvents this problem.[19,20,77] Consistent with this perspective, fluoxetine which has a very long half-life has a much lower propensity to produce withdrawal symptoms than other SSRIs.[77]

To summarize the position, therefore, it is accepted that it is unrealistic to expect the introduction of the 'ideal' antidepressant, which is immediately effective, without side-effects, and non-toxic if taken in overdose by members of this vulnerable patient population. However, despite the undoubted public and media acclaim that the SSRIs, especially fluoxetine, are 'wonder drugs' and an almost indispensable accessory to a stressful 1990s

lifestyle, a more dispassionate analysis reveals that, in the treatment of severe depression, the SSRIs have made very little progress in comparison to the tricyclics which were introduced in the 1950s. SSRIs are no more effective than TCAs (and in severe depression they may even be less effective) and the SSRIs have also not addressed the issue of the delayed onset of efficacy. In side-effect terms, the SSRIs have substituted dry mouth, blurred vision, constipation, sedation and postural hypotension with nausea, vomiting, gastrointestinal disturbance, dizziness, headache and sexual dysfunction; the last is emerging as an increasingly serious problem. Although when taken in overdose, SSRIs are much safer than tricyclics, this advantage needs to be counterbalanced by the finding that the SSRIs can provoke intense suicidal ideation in a small minority of patients, and this often focuses on suicide by violent means. On this basis, it is apparent that while the popularity and acceptance of the SSRIs have advanced the recognition of depression and removed some of its social stigma, the drugs themselves have provided no advance in efficacy and debatable improvements in tolerability and safety in comparison with the TCAs. Later in this chapter, we will describe how pharmaceutical research is tackling the challenge of developing the next generation of antidepressant drugs and what are the chances for achieving therapeutic and commercial success.

The Use of SSRIs to Treat Conditions Other Than Depression

One of the major spin-offs to occur as a result of the overwhelming commercial success of the SSRIs has been the spread of their use not only for severe depression to mild dysthymia, but also to other psychiatric, e.g., bulimia, panic disorder, obsessive-compulsive disorder, anxiety, and non-psychiatric conditions, e.g., obesity, premature ejaculation, Raynaud's syndrome, headache.

The distinction between anxiety and depression was not recognized in the 1950s and it is fair to say that the boundaries between depressive and anxiety states still remain arbitrary and, to some extent, ill-defined.[81] In view of the considerable overlap between these two affective disorders, it is not surprising to discover that, like the tricyclics before them, the SSRIs have been extensively evaluated as treatments for various anxiety-related conditions. Although there is no clear evidence to indicate that the SSRIs will be efficacious in the treatment of generalized anxiety disorder (GAD), the financial rewards to be gained if the SSRIs prove acceptable substitutes for the benzodiazepine anxiolytics is sufficient to entice SmithKline-Beecham (paroxetine), Pharmacia-Upjohn (fluvoxamine), and possibly also Lilly (fluoxetine), into Phase III clinical trials with a view to obtaining regulatory approval for the treatment of GAD. Whilst this strategy is undoubtedly a gamble, there is ample evidence to show that the SSRIs are valuable drugs for the treatment of certain specific anxiety states.

Panic disorder, is now recognized to be a distinct anxiety condition. It has been shown in double-blind, placebo-controlled trials that paroxetine is efficacious in alleviating panic disorder[22,82] and this SSRI has been registered as a treatment for this indication in several territories, including the UK and USA. Positive findings have also been observed in clinical trials of panic disorder with other SSRIs, including fluoxetine,[83] fluvoxamine[84] and citalopram.[85] It is likely that the relevant pharmaceutical companies will also vigorously pursue registration of these other SSRIs as treatments for panic disorder. When comparing the SSRIs in treating panic disorder with the sedative, high efficacy benzodiazepine full agonists, e.g., alprazolam, it is apparent that they have very different time-effect profiles. Whilst the benzodiazepines produce progressive improvement with time, the SSRIs ameliorate panic disorder relatively slowly, often inducing a marked transient increase in panic-related symptomatology during the first week of treatment. Despite this shortcoming, it is anticipated that the SSRIs given in combination with behavioral therapy will gradually replace the benzodiazepines and tricyclics as the first-line treatment for panic disorder.

Social phobia is another anxiety-related condition for which the SSRIs are being evaluated. In open-label, clinical trials, both sertraline and fluoxetine have been reported to be effective for the treatment of social phobia.[86,87] The improvement observed in both trials was moderate. Moreover, efficacy was less pronounced in more socially phobic patients[87] and in those patients where the disorder was of the longest standing.[86] In the more rigorous setting of a double-blind placebo-controlled clinical study, fluoxetine has been shown to produce significant improvements in the anxiety associated with social phobia, but not social avoidance.[88] Based on the limited data available from clinical trials, it is likely that, analogous to their efficacy in alleviating depression, clinically significant amelioration of phobic symptoms will occur only after several weeks of SSRI treatment.

Although on this basis, it would appear that the SSRIs are unlikely to constitute a major step forward in the treatment of these anxiety-related conditions, their relative safety, failure to induce dependence and lack of abuse potential compared with the benzodiazepines are likely to be major factors in promoting their position in the treatment of panic disorder, social phobia and possibly GAD.

The beneficial actions of the serotonin-selective tricyclic antidepressant, clomipramine, in the treatment of obsessive-compulsive disorder[89,90] indicated a potentially specific role for serotonergic systems in the pathogenesis and treatment of this severe and relatively frequent psychiatric condition. It was these observations which prompted the clinical evaluation of various SSRIs in the treatment of obsessive-compulsive disorder. In two large, multicenter, double-blind, placebo-controlled studies, the efficacy of fluoxetine was shown to be statistically superior to placebo with patients showing a 25-35% improvement from their baseline Yale-Brown obsessive-compulsive scale and Clinical Global Improvement scores.[91,92] In the clinical trial conducted by Montgomery and his co-workers, the results favoring fluoxetine over placebo were much less impressive; a result which the investigators attributed to an unusually high placebo response rate.[91] Efficacy of the SSRIs in this psychiatric condition follows a similar, or perhaps even slower, time-course than that observed in depression.[92] Fluoxetine has also been compared with clomipramine in two smaller non-placebo-controlled, double-blind trials, which showed improvements from baseline with both treatments.[93,94] Clomipramine and fluoxetine are both registered in the USA, Europe and other territories for the treatment of obsessive-compulsive disorder. Fluvoxamine has also been shown to have efficacy in treating obsessive-compulsive disorder in six placebo-controlled and four comparator clinical trials[95] and this drug is marketed for this indication both in Europe and the USA. In the latter territory, this is the only disorder for which fluvoxamine has received regulatory approval. Similar efficacy has also been demonstrated for sertraline[96-99] and paroxetine[46,100] and both drugs have been widely approved for the treatment of obsessive-compulsive disorder.

In view of the postulated role of central serotonergic systems in eating disorders and also in the control of food intake, considerable attention has been focused on the potential benefit of the SSRIs in the treatment of bulimia, anorexia and obesity. In view of the compulsive behavioral component in bulimia, it is not surprising that the SSRIs show the greatest benefit in this psychiatric disorder. Double-blind, placebo-controlled clinical trials have demonstrated that high doses of fluoxetine reduce the frequency of binge eating sessions and the number of vomiting episodes.[101-104] Currently, it is the only SSRI to have received regulatory approval for this indication. In contrast, attempts to break into the much more lucrative obesity market have, however, been unsuccessful. There are inconsistencies in the literature with respect to the value of the SSRIs in producing clinically significant weight-loss in obese subjects. Whilst fluoxetine has been reported to reduce the weight of obese subjects,[105-107] clinical trials performed with fluvoxamine[108-110] and citalopram[111] observed no significant benefit of SSRI treatment with respect to placebo and dietary advice. In spite

of the suggestions from short-term clinical trials that fluoxetine may be unique among the SSRIs in having anti-obesity properties, a long-term, double-blind placebo-controlled, clinical trial of fluoxetine showed that its beneficial effect on weight loss at 6 months almost totally disappeared at 12 months.[112] The probable scientific explanation for the failure of the SSRIs in the treatment of obesity is that the potentiation of central serotonergic function induced by reuptake inhibition, e.g., SSRIs, is much less pronounced than that produced by 5-HT releasing agents, e.g., fenfluramine and *d*-fenfluramine.[113,114] Consequently, the SSRIs are unable to provide sufficient serotonergic drive to maintain weight loss. To provide efficacy via monoamine reuptake inhibition, reuptake inhibition of 5-HT has to be combined with that of noradrenaline in order to produce long-term reduction of body weight in obese subjects, c.f., sibutramine (Meridia, Reductil Knoll Pharmaceuticals).

Other conditions where the SSRIs have been suggested to be of therapeutic benefit are premenstrual syndrome, depression resulting from the use of anabolic steroids, anger attacks, post-traumatic stress disorder, borderline personality disorder, trichotillomania, negative symptoms of schizophrenia, cataplexy, depersonalization, autism, paraphilia, alcoholism, chronic headache, migraine prophylaxis, fibrositis, diabetic neuropathy, post-herpetic neuralgia, hypokinetic rigidity syndrome, Raynaud's disease and irritable bowel syndrome.[1,23,46,95,115]

Finally, the pharmaceutical industry, ever adept at turning a disadvantage into an asset, have responded to the increased reporting of SSRI-induced male sexual dysfunction by putting these drugs into clinical development for the treatment of premature ejaculation.

SSRIs in Development

Since the launch of fluoxetine a large number of 5-HT reuptake inhibitors have entered development (see Table 12.5). By the early 1990s, the dominance and success of the SSRIs, fluoxetine (Lilly), sertraline (Pfizer) and paroxetine (SmithKline-Beecham) in the antidepressant marketplace was unquestionable. As a result of the grip which these three SSRIs have on the market, plus the launch of citalopram and the relaunch of fluvoxamine, it is now highly unlikely that additional SSRIs will successfully enter the market. As evidence of this point, the early 1990s saw the withdrawal of many of the SSRIs in development leaving very few remaining (see Table 12.5).

New Strategies for Addressing Key Unmet Needs of Current Antidepressant Drug Therapy

It is clearly paradoxical that the SSRIs inhibit the reuptake of 5-HT almost immediately, but significant clinical improvement requires treatment for 3-8 weeks. This suggests that adaptive mechanisms within the CNS underlie the therapeutic efficacy of the SSRIs rather than reuptake inhibition per se. Recent work indicates a role for serotonergic autoreceptors of the 5-HT_{1A} and 5-HT_{1B} subtypes in the mechanism of action of the SSRIs (see also: Chapter 9). Thus, it has been postulated that the delay in therapeutic efficacy with the SSRIs results from activation of neuronal homeostatic mechanisms which blunt the actions of the SSRIs to enhance central serotonergic drive. Thus, increased extraneuronal 5-HT concentration produced by the SSRIs activates both somato-dendritically located 5-HT_{1A} autoreceptors in the raphé and prejunctional 5-HT_{1B} receptors in the terminal fields. These autoreceptor systems then switch off neuronal firing and terminal 5-HT release and this severely impedes the potentiating effect of 5-HT reuptake inhibition. It is only when 5-HT_{1A} and 5-HT_{1B} autoreceptors are desensitized that the SSRIs produce their full pharmacological effect; it is this time-course which has been postulated to account for the delay in therapeutic effect with the SSRIs (for a review see ref. 116 and Chapter 9).

Clinical trials have shown that the antidepressant efficacy of the SSRIs is improved by the addition of pindolol.[117-120] Pindolol has affinity not only for β_1- and β_2-adrenoceptors, but also 5-HT_{1A} receptors.[121] Thus, it has been postulated that pindolol augments the antidepressant effects of the SSRIs by antagonizing the auto-inhibitory effects of 5-HT at somato-dendritically located 5-HT_{1A} receptors.[117,122] This hypothesis is supported by both electrophysiological and in vivo microdialysis data. Pindolol reverses the SSRI-induced decrease in the firing activity of serotonergic neurons.[123-125] Furthermore, 5-HT_{1A} antagonists potentiate the increase in extracellular 5-HT concentrations produced by SSRIs.[124-129] Thus, one strategy that has been adopted in the search for antidepressants which are more rapidly acting and efficacious in treatment-resistant patients is to combine 5-HT_{1A} antagonism with 5-HT reuptake inhibition. This has resulted in several companies filing patents claiming combinations of 'named' SSRIs and SNRIs, e.g., fluoxetine, citalopram, fluvoxamine and duloxetine, and 'named' 5-HT_{1A} antagonists, e.g., pindolol and WAY100635. These include Eli Lilly (EP-687472-1995; EP-714663-1996; EP-759299-1997), Astra (WO9633710-1996) and American Home Products (GB2303303-1997) which have been reviewed by Kerrigan.[130] However, due to the extensive prior art in this area, it is unclear whether these patent applications will be granted.

Despite its attractiveness, a number of issues relating to this hypothesis remain to be reconciled. 5-HT_{1A} receptors are located both presynaptically on the soma and dendrites of serotonergic neurons, and postsynaptically on other cell types in the terminal regions, e.g., limbic, cortical and hypothalamic areas.[131,132] Postsynaptically located 5-HT_{1A} receptors have been implicated in the antidepressant actions of the SSRIs (for a review see refs. 116, 133). Thus, antagonist actions at 5-HT_{1A} receptors located postsynaptically would be expected to counterbalance the beneficial effects of enhanced serotonergic neurotransmission resulting from blockade of somato-dendritic 5-HT_{1A} receptors in the raphé. The ideal drug would therefore combine 5-HT_{1A} autoreceptor antagonism and 5-HT reuptake inhibition, with no inhibition of postsynaptic 5-HT_{1A} receptors. Interestingly, pindolol has been reported to block the inhibitory effects of 5-HT on somatodendritic 5-HT_{1A} receptors, but not the hyperpolarizing effects on CA_3 pyramidal cells of the hippocampus mediated through postsynaptic 5-HT_{1A} receptors.[123,125] Thus, electrophysiological data suggest that pindolol selectively blocks somatodendritic 5-HT_{1A} autoreceptors. However, the pharmacological activity of pindolol at 5-HT_{1A} receptors remains controversial. For example, pindolol has been shown to act as a 5-HT_{1A} antagonist at postsynaptically located receptors[134-136] and to exhibit 5-HT_{1A} agonist-like effects in some models.[137-142] Finally, the possibility remains that pindolol may exert its effect not through 5-HT_{1A} receptors, but via its actions as a β-adrenoceptor partial agonist.

An alternative strategy involving 5-HT_{1A} receptors is to combine 5-HT_{1A} full agonism with 5-HT reuptake inhibition. This approach is based on the hypothesis that a 5-HT_{1A} full agonist will produce rapid desensitization of somatodendritic 5-HT_{1A} autoreceptors and will concurrently activate postsynaptically located 5-HT_{1A} receptors directly, thereby counteracting the initial decrease in serotonergic function due to activation of 5-HT_{1A} autoreceptors (for a review see ref. 133).

Several companies have filed patents which claim sets of compounds combining 5-HT_{1A} receptor affinity and 5-HT reuptake inhibition in the same molecule; they include Bristol-Myers Squibb, American Home Products, Knoll Pharmaceuticals, and Lundbeck (for a review see ref. 130). However, we are aware of only one compound which possesses this pharmacological profile that is in clinical development, viz., EMD 68843 (E Merck). Interestingly, EMD 68843 purportedly combines 5-HT reuptake inhibition with selective presynaptic 5-HT_{1A} receptor agonism.[143] EMD 68843 is currently in Phase II clinical trials and the results are eagerly awaited.

Table 12.5. Development status of newer SSRIs

Name/Compound number	Pharmacological profile	Company (country)	Phase in development	Date discontinued
Cianopramine	5-HT reuptake inhibitor	Roche (Switzerland)	Phase III	January 1991
Levoprotiline	5-HT reuptake inhibitor/ H_1 antagonist	Novartis (Switzerland)	Phase III	1993
Litoxetine	5-HT reuptake inhibitor/ 5-HT_3 antagonist	Synthelabo (France)	Phase II/III	February 1994
Femoxetine	5-HT reuptake inhibitor	Novo Nordisk (Denmark)	Phase III	December 1996
Cericlamine	5-HT reuptake inhibitor	Jouveinal (France)	Phase III	
Sercloremine	5-HT reuptake inhibitor/ MAO-A inhibitor	Novartis (Switzerland)	Phase II	February 1992
Ifoxetine	5-HT reuptake inhibitor	Novartis (Switzerland)	Phase II	August 1992
BMS 181101/BMY 42569	5-HT reuptake inhibitor $5\text{-HT}_{1A/1D}$ agonist	Bristol-Myers Squibb (USA)	Phase II	October 1995

Table 12.5., cont. Development status of newer SSRIs

Name/Compound number	Pharmacological profile	Company (country)	Phase in development	Date discontinued
Dapoxetine	5-HT reuptake inhibitor	Eli Lilly (USA)	Phase II	1996
Tandamine	5-HT reuptake inhibitor	American Home Products (USA)	Phase II?	
EMD 48117	5-HT reuptake inhibitor	Merck KGaA (Germany)	Phase I	March 1987
CGS 10686	5-HT reuptake inhibitor	Novartis (Switzerland)	Phase I	October 1991
FG 7080	5-HT reuptake inhibitor	Novo Nordisk (Denmark)	Preclinical	March 1989
Efetaxole	5-HT reuptake inhibitor	Novartis (Switzerland)	Preclinical	February 1990
CGP 6085A	5-HT reuptake inhibitor	Novartis (Switzerland)	Preclinical?	February 1991
RP 68303	5-HT reuptake inhibitor	Rhone-Poulenc Rorer (France)	Preclinical	March 1992

Table 12.5., cont. Development status of newer SSRIs

Name/Compound number	Pharmacological profile	Company (country)	Phase in development	Date discontinued
FCE 25876	5-HT reuptake inhibitor	Pharmacia-Upjohn (Italy)	Preclinical	June 1992
VUFB 17070	5-HT reuptake inhibitor	VUFB (Czechoslovakia)	Preclinical	December 1992
FI 4500	5-HT reuptake inhibitor	Ferrer (Spain)	Preclinical	July 1996
Indeloxazine analogues	5-HT reuptake inhibitor 5-HT_2 antagonist	Yamanouchi (Japan)	Preclinical	March 1997
709W92	5-HT reuptake inhibitor Tryptophan 2,3-dioxygenase inhibitor	Glaxo-Wellcome (UK)	Preclinical	
A 80426	5-HT reuptake inhibitor α2-adrenoceptor antagonist	Abbott (USA)	Preclinical	
YM 35992/YM 992	5-HT reuptake inhibitor 5-HT_{2A} receptor antagonist	Yamanouchi	Preclinical/Phase 1	

The second strategy which has been adopted to circumvent the auto-inhibitory actions of the SSRIs is to combine 5-HT_{1B} antagonism with 5-HT reuptake inhibition. Preclinical data to support this approach are limited and based on the finding that the 5-$HT_{1B/1D}$ antagonist, GR 127935, potentiates the increase in 5-HT efflux produced by the SSRIs.[144-146] The absence of clinical data is due to the lack of suitable pharmacological tools. Pfizer have filed patents claiming combinations of the SSRI, sertraline, with 5-HT_{1B} agonists or antagonists (WO9603400-1996 and EP-701819 A2-1996). Pierre Fabre have also filed a patent claiming combinations of the SNRI, milnacipran, with 5-$HT_{1B/1D}$ antagonists (WO9728141-1997). There are few patent filings claiming series of compounds combining 5-HT_{1B} receptor affinity and 5-HT reuptake inhibition in the same molecule, with no compounds currently in clinical development.

Two other 5-HT based approaches are being pursued with the aim of identifying antidepressant drugs which are more rapidly acting and efficacious in treatment-resistant patients. The first involves blockade of both 5-HT_{1A} and 5-HT_{1B} autoreceptors to increase 5-HT neuronal firing and terminal 5-HT release, respectively. Preclinical data to support this approach are limited to a single microdialysis study demonstrating that the combination of the 5-HT_{1A} receptor antagonist, WAY 100635, and the 5-$HT_{1B/1D}$ antagonist, GR 127935, leads to a dramatic increase in extraneuronal 5-HT in the frontal cortex of guinea-pigs.[147] SmithKline-Beecham have filed a patent claiming combinations of 'named' 5-HT_{1A} receptor antagonists, e.g., WAY 100635 and 5-HT_{1B} antagonists, e.g., GR 127935 (WO9531988-A). Several companies have filed patents claiming series of compounds with combined 5-HT_{1A} and 5-HT_{1B} receptor affinity, including SmithKline-Beecham, Eli Lilly, Merrell-Dow, Pierre Fabre, Synthélabo, Duphar, Knoll Pharmaceuticals and Pfizer (for a review see ref. 130). However, many of these patents relate to agonists rather than antagonists. There would appear to be no compounds with this pharmacological profile in clinical development at this point in time.

The second approach differs from the others in that it involves enhanced serotonergic and noradrenergic neurotransmission. This is achieved by the combination of 5-HT_{1A} receptor agonism and α_2-adrenoceptor antagonism. As already discussed, 5-HT_{1A} agonists enhance serotonergic function by stimulating postsynaptic 5-HT_{1A} receptors. This has been postulated to more than compensate for the decrease in 5-HT neuronal firing resulting from activation of 5-HT_{1A} autoreceptors in the raphé (for a review see ref. 133). 5-HT_{1A} receptor agonists have also been reported to enhance central noradrenergic function by decreasing 5-HT neuronal firing in the raphé, which results in increased firing of noradrenergic neurons in the locus coeruleus.[148,149] α_2-Adrenoceptor antagonists increase noradrenergic function by blocking the inhibitory effects of noradrenaline at α_2-autoreceptors located on noradrenergic cell bodies and nerve terminals, thereby preventing noradrenaline from inhibiting its own release.[150-152] Sunipetron (CP-93,393, Pfizer) is a 5-HT_{1A} receptor agonist/α_2-antagonist which is currently in Phase II trials for depression and anxiety.

Sunipetron has been shown to act as a potent agonist at 5-HT_{1A} autoreceptors, but to display only moderate affinity for postsynaptic 5-HT_{1A} receptors.[153,154] It exhibits α_2-adrenoceptor antagonist activity in rat brain and CHO (chinese hamster ovary) cells expressing the human α_{2A}-adrenoceptor.[153,154] No other compounds would appear to be in clinical development.

These are the approaches which in the short-term have the potential to deliver a rapidly acting antidepressant demonstrating efficacy in treatment-resistant patients, thereby addressing the two key unmet needs of current antidepressant therapy. However, these approaches are not without risk. As already stated, antagonism at postsynaptically located receptors, in particular the 5-HT_{1A} subtype, may be counter-productive in terms of

antidepressant efficacy. Dialysis studies demonstrate that approaches including autoreceptor antagonism produce very large increases in extracellular 5-HT levels in comparison to the SSRIs. The SSRIs are associated with a number of side-effects which result from enhanced central serotonergic function. Thus, the problems of nausea, gastrointestinal disturbance (vomiting and diarrhea), headache, sedation, dizziness, agitation and sexual dysfunction are likely to be exacerbated. Side-effects are likely to be less of an issue with regard to those approaches involving 5-HT_{1A} agonism. However, full agonism appears to be required for antidepressant efficacy[133] and only a handful of 5-HT_{1A} full agonists have been identified to date. A major issue for all strategies is clear clinical data to demonstrate rapid onset of action and efficacy in treatment-resistant patients that will be acceptable to the regulatory authorities. The design of clinical trials to assess the early onset of antidepressant action is controversial.[155-159] The definition of treatment-resistant patients is also far from clear. Large placebo responses have consistently confounded the results of clinical trials with antidepressants. In the double-blind, placebo-controlled study of pindolol with fluoxetine performed by Pérez and co-workers,[119] a single-blind placebo run-in phase to eliminate placebo responders who could artifactually increase the response rate was performed. Despite this precaution, the shorter time to sustained response in the patients treated with fluoxetine plus pindolol clearly could not be attributed to a higher response rate in this group or a faster improvement in the patients who responded. Thus, the design of clinical trials will also be crucial to the success of these approaches.

SSRIs: Current and Future Status

Having critically evaluated the contribution which the SSRIs have made to the treatment of a multiplicity of psychiatric and non-psychiatric disorders and, in addition, the strategies which the pharmaceutical industry are adopting in order to develop the successors to the SSRIs, it is now appropriate to consider the challenges ahead and the likelihood of therapeutic and commercial success.

It is evident that the deficiencies of the SSRIs in the treatment of depression leave ample opportunity for the introduction of advantaged antidepressant drugs. With efficacy, the issues remain of delay in onset of antidepressant action, incomplete efficacy in a significant proportion of more severely depressed patients and non-responsiveness to SSRI therapy. It is also clear from experiences with the SSRIs that, despite their enviable reputation as 'wonder drugs', they have failed in every instance to demonstrate consistent, statistical (or therapeutic) improvements in comparative trials of efficacy against the tricyclics. Earlier in the chapter, we have elucidated the problems associated with the appropriate selection of patients for inclusion in comparative trials and the necessity for rigorous control to avoid excessive placebo responding in the clinical trial setting. These strictures have ensured that currently there are only a very few trials, all with relatively small patient populations, which have demonstrated the superiority of SSRI treatment in combination with, for example pindolol, in comparison to SSRI treatment alone. Clinical trial design to reduce placebo response rates have involved putting all depressed subjects onto placebo treatment and eliminating those with markedly positive responses at the end of this run-in phase, prior to randomization on drug or placebo treatment. This type of protocol is unlikely to be acceptable in a regulatory submission. Using conventional clinical trial protocols, it is often difficult to demonstrate antidepressant efficacy in double-blind placebo-controlled studies, and to date, it has been almost impossible to show superiority against comparator antidepressants. This problem remains a major stumbling-block for the development of the next generation of antidepressants. Venlafaxine (Effexor, American Home Products) and duloxetine (Lilly) both serve as examples of the difficulties in this area. Venlafaxine and duloxetine are 'second generation' serotonin and noradrenaline reuptake inhibitors (SNRIs). They were developed partly on the basis

that combined reuptake inhibition of both monoamines would provide antidepressants which were more effective than the SSRIs. (The basis for this hypothesis being anecdotal evidence that the tricyclics may be more efficacious than the SSRIs in the treatment of severe depression). Attempts to claim that venlafaxine is a rapidly acting antidepressant on the basis of early improvement in selected items in various depression rating scales have been firmly rebuffed by the regulatory authorities. Without this key marketing claim, venlafaxine has made little impact on sales of the SSRIs in the USA and Europe (Table 12.6). Similarly, Lilly's withdrawal of duloxetine from development as an antidepressant is rumored to have been linked to its failure to show better efficacy than their flagship SSRI, fluoxetine.

This fate may not befall some of the other newer pharmacological approaches currently being pursued by the pharmaceutical industry. However, those targeted at improving antidepressant efficacy by increasing serotonergic drive to levels beyond those achievable with SSRIs are at risk of being poorly tolerated in patients because of the intensity of their side-effects, especially at the initiation of treatment. In fact, one has to question whether such powerful antidepressants are appropriate for the treatment of patients at the mild to moderate end of the depression spectrum.

If one accepts the premise that genuinely improved antidepressants will enter the market over the next 5-7 years, the question then becomes, will they be commercially successful? The outcome here is dependent on several key factors. The size of the marketing investment and sales force will be critical. Having a better alternative to the SSRIs is not enough, opinion leaders, psychiatrists, general practitioners and the public must be aware of this fact and accept it. In view of the broad acceptance and satisfaction with the SSRIs, this will be a very difficult process to manage and it is one which could only be attempted by a major pharmaceutical industry player, preferably one with an established position in the antidepressants market, e.g., Lilly, Pfizer, SmithKline-Beecham. Evidence for this comes from the observation that although Solvay-Duphar launched fluvoxamine before Lilly's fluoxetine, it was the pharmaceutical industry giant, Lilly, which revolutionized the antidepressants market. From a strategic viewpoint, it would also make sense for an advantaged antidepressant to be launched by a company which already markets a very successful SSRI. This is because the new drug could then be positioned as a premium-priced product for use in patients who are severely depressed, vulnerable to suicide or resistant to conventional antidepressant therapy. Taking market share from low-cost, generic SSRIs would then be dependent on the margin of advantage over the SSRIs which the new antidepressants are perceived to possess. The plateau in the number of antidepressant prescriptions (Fig. 12.5) indicates that there is unlikely to be much additional market growth as a result of either increased diagnosis of depression or use of antidepressants in the treatment of other disorders. This again implies that for major commercial success, any newly introduced antidepressant will have to gain a major portion of the low-cost, generic SSRI market.

In summary, therefore, the path for the advantaged antidepressant is littered with challenging hurdles, i.e., scientific, clinical, commercial and educational, and it is almost impossible to predict at this stage whether the next generation of antidepressants will successfully negotiate them and go on to become 'blockbusters', like the SSRIs. It is our belief that circumstance and public attitudes play a critical role in this process and as long as the SSRIs remain trusted, effective antidepressants, it is unlikely that new introductions will have the same impact as the SSRIs. If this perception was to change radically as a result of serious adverse effects occurring in patients, then the climate for new antidepressant introductions would markedly improve. In view of the length of time which the SSRIs have been on the market and the number of patient exposures, this is not a likely outcome. However, as shown by the sudden fall from grace of the benzodiazepines, such things do

Table 12.6. 1997—Relative sales of leading antidepressants in the USA and Europe

		USA		Europe	
Antidepressant	**Class**	**Sales [£(sterling) millions]**	**Market Position**	**Sales [£(sterling) millions]**	**Market Position**
Fluoxetine	SSRI	1,112	1st	250	1st
Sertraline	SSRI	691	2nd	90	4th
Paroxetine	SSRI	549	3rd	202	2nd
Citalopram	SSRI	-	-	101	3rd
Venlafaxine	SNRI	129	4th	40	5th
Fluoxetine	SSRI	68	7th	26	9th

happen. In the absence of such an event, it is likely that improved antidepressants will be introduced to treat depression more effectively than either the SSRIs or the tricyclics. If marketed astutely, they are also likely to be commercially successful; whether they will be 'blockbusters', only time will tell.

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References

1. Wong DT, Bymaster FP, Engleman EA. Prozac (fluoxetine, Lilly 110140), the first selective serotonin uptake inhibitor and an antidepressant drug: Twenty years since its first publication. Life Sci 1995; 57:411-441.
2. Zeller EA, Barsky J, Fouts JR et al. Influence of isonicotinic acid hydrazide (INH) and isonicotinoyl-2-isopropylhydrazine (IIH) on bacterial and mammalian enzymes. Experientia 1952; 8:349-350.
3. Selikoff IJ, Robitzek EH, Ornstein GG. Toxicity of hydrazine derivatives of isonicotinic acid in the chemotherapy of human tuberculosis. Quart Bull Sea View Hosp 1952; 13:17-26.
4. Glowinski J, Axelrod J. Inhibition of uptake of tritiated-noradrenaline in the intact rat brain by imipramine and structurally related compounds. Nature 1964; 204:1318-1319.
5. Carlsson A, Fuxe K, Hamberger B et al. Biochemical and histochemical studies on the effects of imipramine-like drugs and (+)-amphetamine on central and peripheral catecholamine neurons. Acta Physiol Scand 1966; 67:481-497.
6. Kuhn R. The treatment of depressive states with G22355 (imipramine hydrochloride). Am J Psychiatry 1958; 115:459-464.
7. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry 1965; 122:509-522.

8. Bunney WE, Davis JM. Norepinephrine in depressive reactions. Arch Gen Psychiatry 1965; 13:483-494.
9. Coppen A. The biochemistry of affective disorders. Br J Psychiatry 1967; 113:1237-1264.
10. Lapin IP, Oxenkrug GF. Intensification of the central serotoninergic processes as a possible determinant of the thymoleptic effect. Lancet 1969; i:132-136.
11. Curzon G. Tryptophan pyrrolase—A biochemical factor in depressive illness. Br J Psychiatry 1969; 115:1367-1374.
12. Prien RF, Carpenter LL, Kupfer DJ. The definition and operational criteria for treatment outcome of major depressive disorder. A review of the current research literature. Arch Gen Psychiatry 1991; 48:796-800.
13. Bechelli LP, Nardi AE, Alves AB. Review on the use of irreversible monoamine oxidase inhibitors (MAOIs) in psychiatry. Curr Med Res Opin 1989; 11:38-52.
14. Heal DJ, Buckett WR. Development of antidepressant drugs for the 1990s: Progress or procrastination? Int J Ger Psychiatry 1991; 6:431-443.
15. Rudorfer MV. Monoamine oxidase inhibitors: reversible and irreversible. Psychopharmacol Bull 1992; 28:45-57.
16. Brotman AW, Falk WE, Gelenberg AJ. Pharmacologic treatment of acute depressive subtypes. In: Meltzer HY, ed. Psychopharmacology. The third generation of progress. New York: Raven Press, 1987:1031-1040.
17. Klerman GL, Cole JO. Clinical pharmacology of imipramine and related antidepressant compounds. Pharmacol Rev 1965; 17:101-141.
18. Morris JB, Beck AT. The efficacy of antidepressant drugs. Arch Gen Psychiatry 1974; 130:1022-1024.
19. Davis JM. Tricyclic antidepressants. In: Simpson LL, ed. Drug Treatment of Mental Disorders. New York: Raven Press, 1975:127-146.
20. Kupfer DJ, Detre TP. Tricyclic and monoamine oxidase-inhibitor antidepressants: clinical use. In: Iversen LL, Iversen SD, Snyder SH, ed(s). Handbook of Psychopharmacology. Affective Disorders: Drug actions in animals and man. Vol. 14. New York: Plenum Press, 1978:199-232.
21. Cohn JB, Wilcox C. A comparison of fluoxetine, imipramine, and placebo in patients with major depressive disorder. J Clin Psychiatry 1985; 46:26-31.
22. Dunbar GC, Claghorn JL, Kiev A et al. A comparison of paroxetine and placebo in depressed outpatients. Acta Psychiatr Scand 1993; 87:302-305.
23. Finley PR. Selective serotonin reuptake inhibitors: Pharmacological profiles and potential therapeutic distinctions. Ann Pharmacother 1994; 28:1359-1369.
24. Gram LF. Fluoxetine. New Eng J Med. 1994; 331:1354-1361.
25. Lane R, Baldwin D, Preskorn S. The SSRIs: Advantages, disadvantages and differences. J Psychopharmacol 1995; 9:163-178.
26. Montgomery SA, Johnson FN. Citalopram in the treatment of depression. Rev Contemp Pharmacother 1995; 6:297-306.
27. Edwards JG. Drug choice in depression: Selective serotonin reuptake inhibitors or tricyclic antidepressants? CNS Drugs 1995; 4:141-159.
28. Bremner JD. Fluoxetine in depressed patients: A comparison with imipramine. J Clin Psychiatry 1984; 45:414-419.
29. Feighner JP, Cohn JB. Double-blind comparative trials of fluoxetine and doxepin in geriatric patients with major depressive disorder. J Clin Psychiatry 1985; 46:20-25.
30. Masco HL, Sheetz MA. Double-blind comparison of fluoxetine and amitriptyline in the treatment of major depressive illness. Adv Therapy 1985; 2:275-284.
31. Feighner JP, Boyer WF. Paroxetine in the treatment of depression: A comparison with imipramine and placebo. Acta Psychiatr Scand 1989; 80:125-129.
32. Aguglia E, Casacchia M, Cassano GB et al. Double-blind study of the efficacy and safety of sertraline versus fluoxetine in major depression. Int Clin Psychopharmacol 1993; 8:197-202.
33. Ansseau M, Gabriëls A, Loyens J et al. A double-blind comparison of paroxetine and fluvoxamine in major depression. Eur Neuropsychopharmacol 1993; 3:323-324.

34. Bennie EH. Double-blind study of sertraline and fluoxetine in outpatients with major depression. Presented at the 9th World Congress of Psychiatry, Rio de Janeiro, Brazil, 6-12 June, 1993.
35. De Wilde J, Spiers R, Mertens C et al. A double-blind, comparative, multicentre study comparing paroxetine with fluoxetine in depressed patients. Acta Psychiatr Scand 1993; 87:141-145.
36. Geretsegger C, Böhmer F, Ludwig M. Paroxetine in the elderly depressed patient: Randomized comparison with fluoxetine of efficacy, cognitive and behavioural effects. Int Clin Psychopharmacol 1994; 9:25-29.
37. Tignol J. A double-blind, randomized, fluoxetine-controlled, multicenter study of paroxetine in the treatment of depression. J Clin Psychopharmacol 1993; 13:18S-22S.
38. Zarate CA, Kando JC, Tohen M et al. Does intolerance or lack of response with fluoxetine predict the same will happen with sertraline? J Clin Psychiatry 1996; 57:67-71.
39. Shein K, Smith SE. Structure activity relationships for the anticholinoceptor action of tricyclic antidepressants. Br J Pharmacol 1978; 62:567-571.
40. Tang SW, Seeman P. Effect of antidepressant drugs on serotonergic and adrenergic receptors. Naunyn-Schmiedeberg's Arch Pharmacol 1980; 311:255-261.
41. Richelson E, Nelson A. Antagonism by antidepressants of neurotransmitter receptors of normal human brain in vitro. J Pharmacol Exp Ther 1984; 230:94-102.
42. Heal DJ, Cheetham SC, Martin KF et al. Comparative pharmacology of dothiepin, its metabolites, and other antidepressant drugs. Drug Dev Res 1992; 27:121-135.
43. Tollefson GD. Antidepressant treatment and side-effect considerations. J Clin Psychiatry 1991; 52:S4-S13.
44. Wong DT, Bymaster FP, Reid LR et al. Fluoxetine and two other serotonin uptake inhibitors without affinity for neuronal receptors. Biochem Pharmacol 1983; 32:1287-1293.
45. Cusack B, Nelson A, Richelson E. Binding of antidepressants to human brain receptors: focus on new generation compounds. Psychopharmacology 1994; 114:559-565.
46. Corby CL, Dunne G. Paroxetine: A review. J Serotonin Res 1997; 4:47-64.
47. Foster RH, Goa KL. Paroxetine: A review of its pharmacology and therapeutic potential in the management of panic disorder. CNS Drugs 1997; 8:163-188.
48. Denckar SJ, Petersen HEH. Side-effect profile of citalopram and reference antidepressants in depression. Proc XXII Nordiske Psykiater-Kongres Reykjavik, Excerpta Medica, Amsterdam: 1988:31-42.
49. Rickels K, Schweizer E. Clinical overview of serotonin reuptake inhibitors. J Clin Psychiatry 1990; 51:9-12.
50. Grimsley SR, Jann MW. Paroxetine, sertraline, and fluoxetine: New selective serotonin re-uptake inhibitors. Clin Pharmacy 1992; 11:930-957.
51. Wagner W, Plekkenpol B, Gray TE et al. Review of fluvoxamine safety database. Drugs 1992; 43:48-54.
52. Zajecka J, Fawcett J, Schaff M et al. The role of serotonin in sexual dysfunction: fluoxetine-associated orgasm dysfunction. J Clin Psychiatry 1991; 52:66-68.
53. Walker PW, Cole JO, Gardner EA et al. Improvement in fluoxetine-associated sexual dysfunction in patients switched to bupropion. J Clin Psychiatry 1993; 54:459-465.
54. Modell JG, Katholi CR, Modell JD et al. Comparative sexual side-effects of bupropion, fluoxetine, paroxetine, and sertraline. Clin Pharmacol Ther 1997; 61:476-487.
55. Cookson J. Side-effects of antidepressants. Br J Psychiatry 1993; 163:20-24.
56. Anderson IM, Tomenson BM. Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: A meta-analysis. Br Med J 1995; 310:1433-1438.
57. Crome P, Newman B. Fatal tricyclic antidepressant poisoning. J Royal Soc Med 1979; 72:649-653.
58. Leonard BE. Toxicity of antidepressants. Lancet 1986; ii:1105.
59. Cassidy S, Henry J. Fatal toxicity of antidepressant drugs in overdose. Br Med J 1987; 295:1021-1024.

60. Henry JA. A fatal toxicity index for antidepressant poisoning. Acta Psychiatr Scand 1989; 80:37-45.
61. Guze SB, Robins E. Suicide and primary affective disorders. Br J Psychiatry 1970; 117:437-438.
62. Henry JA, Antao CA. Suicide and fatal antidepressant poisoning. Eur J Med 1992; 1:343-348.
63. Harrison G. New or old antidepressants? New is better. Br Med J 1994; 309:1280-1282.
64. Isacsson G, Bergman U, Rich CL. Antidepressants, depression and suicide: An analysis of the San Diego study. J Affect Disord 1994; 32:277-286.
65. Owens D. Benefits of new drugs are exaggerated. Br Med J 1994; 309:1281-1282.
66. Hotopf M, Lewis G, Normand C. Are SSRIs a cost-effective alternative to tricyclics? Br J Psychiatry 1996; 168:404-409.
67. Teicher MH, Glod C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. Am J Psychiatry 1990; 147:207-210.
68. Teicher MH, Glod C, Cole JO. Antidepressant drugs and the emergence of suicidal tendencies. Drug Safety 1993; 8:186-212.
69. Rothschild AJ, Locke CA. Reexposure to fluoxetine after serious suicide attempts by three patients: the role of akathisia. J Clin Psychiatry 1991; 52:491-493.
70. Wirshing W, Van Putten T, Rosenberg JF et al. Fluoxetine, akathisia and suicidality: Is there a causal connection? Arch Gen Psychiatry 1992; 49:580-581.
71. Beasley CM, Dornseif BE, Bosomworth JC et al. Fluoxetine and suicide: A meta-analysis of controlled trials of treatment for depression. Br Med J 1991; 303:685-692.
72. Beasley CM, Dornseif BE, Bosomworth JC et al. Fluoxetine and suicide: A meta-analysis of controlled trials of treatment for depression. Int Clin Psychopharmacol 1992; 6:35-57.
73. Fulton B, McTavish D. Fluoxetine: An overview of its pharmacodynamic and pharmacokinetic properties and review of its therapeutic efficacy in obsessive-compulsive disorder. CNS Drugs 1995; 3:305-322.
74. Szabadi E. Fluvoxamine withdrawal syndrome. Br J Psychiatry 1992; 160:283-284.
75. Louie AK, Lannon RA, Ajari LJ. Withdrawal reaction after sertraline discontinuation. Am J Psychiatry 1994; 151:450-451.
76. Kent LSW, Laidlaw JDD. Suspected congenital sertraline dependence. Br J Psychiatry 1995; 167:412-413.
77. Lane RM. Withdrawal symptoms after discontinuation of selective serotonin reuptake inhibitors (SSRIs). J Serotonin Res 1996; 3:75-83.
78. Dilsaver SC, Davidson R. Cholinergic properties of desipramine and amoxapine: assessment using a thermoregulation paradigm. Prog Neuro-Psychopharmacol Biol Psychiatry 1987; 11:581-599.
79. Wolfe RM. Antidepressant withdrawal reactions. Am Family Physician 1997; 56:455-462.
80. Pyke RE. Paroxetine withdrawal syndrome. Am J Psychiatry 1995; 152:149-150.
81. Tyrer P. Anxiety and depression: A clinical profile. In: Elliott JM, Heal DJ, Marsden CA, eds. Experimental approaches to anxiety and depression. Chichester: John Wiley, 1992:9-23.
82. Oehrberg S, Christiansen PE, Behnke K et al. Paroxetine in the treatment of panic disorder. A randomised, double-blind, placebo-controlled study. Br J Psychiatry 1995; 167:374-379.
83. Gorman JM, Liebowitz MR, Fryer AJ et al. An open trial of fluoxetine in the treatment of panic attacks. J Clin Psychopharmacol 1987; 7:329-332
84. Westenberg HGM, den Boer JA. New findings in the treatment of panic disorder. Pharmacopsychiatry 1993; 26:30-33.
85. Humble M, Wistedt B. Serotonin, panic disorder and agoraphobia: Short-term and long-term efficacy of citalopram in panic disorders. Int Clin Psychopharmacol 1992; 6:21-39.
86. Van Ameringen M, Mancini C, Streiner DL. Fluoxetine efficacy in social phobia. J Clin Psychiatry 1993; 54:27-32.
87. Czepowicz VD, Johnson MR, Lydiard RB et al. Sertraline in social phobia. J Clin Psychopharmacol 1995; 15:372-373.

88. Van Vliet IM, den Boer JA, Westenberg HGM. Psychopharmacological treatment of social phobia: A double-blind placebo controlled study with fluvoxamine. Psychopharmacology 1994; 115:128-134.
89. Thorén P, Åsberg M, Cronholm B et al. Clomipramine treatment of obsessive-compulsive disorder. I. A controlled clinical trial. Arch Gen Psychiatry 1980; 37:1281-1285.
90. Murphy DL, Zohar J, Benkelfat C et al. Obsessive-compulsive disorder as a 5-HT subsystem-related behavioural disorder. Br J Psychiatry 1989; 155:15-24.
91. Montgomery SA, McIntyre A, Osterheider M et al. A double-blind, placebo-controlled study of fluoxetine in patients with DSM-III-R obsessive-compulsive disorder. Eur Neuropsychopharmacol 1993; 3:143-152.
92. Tollefson GD, Rampey AH, Potvin JH et al. A multicenter investigation of fixed-dose fluoxetine in the treatment of obsessive-compulsive disorder. Arch Gen Psychiatry 1994; 51:559-567.
93. Pigott TA, Pato MT, Bernstein SE et al. Controlled comparisons of clomipramine and fluoxetine in the treatment of obsessive-compulsive disorder. Behavioral and biological results. Arch Gen Psychiatry 1990; 47:926-932.
94. Saiz Ruiz J, Ibor-López JJ, Cottreaux J et al. Double-blind comparison of fluoxetine and clomipramine in obsessive-compulsive disorder. Eur Neuropsychopharmacol 1992; 2:204-205.
95. Palmer KJ, Benfield P. Fluvoxamine: An overview of its pharmacological properties and review of its therapeutic potential in non-depressive disorders. CNS Drugs 1994; 1:57-87.
96. Griest JH, Jefferson JW, Kobak KA et al. A 1 year double-blind placebo-controlled fixed dose study of sertraline in the treatment of obsessive-compulsive disorder. Int Clin Psychopharmacol 1995a; 10:57-65.
97. Griest JH, Chouinard G, DuBoff E et al. Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder. Arch Gen Psychiatry 1995b; 52:289-295.
98. Wolkow R, March J, Safferman A et al. A placebo-controlled trial of sertraline treatment for pediatric obsessive-compulsive disorder. Biol Psychiatry 1997; 42:213S.
99. Perry CM, Benfield P. Sertraline: An overview of its pharmacological properties and a review of its therapeutic efficacy in obsessive-compulsive disorder. CNS Drugs 1997; 7:480-500.
100. Zohar J, Judge R and the OCD Paroxetine Study Investigators. Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. Br J Psychiatry 1996; 169:468-474.
101. Freeman CPL, Hampson M. Fluoxetine as a treatment for bulimia nervosa. Int J Obes 1987; 11:171-177.
102. Fichter MM, Liebl K, Rief W et al. Fluoxetine versus placebo: A double-blind study with bulimic inpatients undergoing intensive psychotherapy. Pharmacopsychiatry 1991; 24:1-7.
103. Marcus MD, Wing RR, Ewing L et al. A double-blind placebo-controlled trial of fluoxetine plus behavior modification in the treatment of obese binge-eaters and non-binge-eaters. Am J Psychiatry 1990; 147:876-881.
104. Fluoxetine Bulimia Nervosa Collaborative Study Group. Fluoxetine in the treatment of bulimia nervosa. A multicenter, placebo-controlled, double-blind trial. Arch Gen Psychiatry 1992; 49:139-147.
105. Ferguson JM, Feighner JP. Fluoxetine-induced weight loss in overweight non-depressed humans. Int J Obes 1987; 11:163-170.
106. Levine LR, Rosenblatt S, Bosomworth J. Use of a serotonin re-uptake inhibitor, fluoxetine, in the treatment of obesity. Int J Obes 1987; 11:185-190.
107. Levine LR, Enas GG, Thompson WL et al. Use of fluoxetine, a selective serotonin-uptake inhibitor, in the treatment of obesity: A dose-response study. Int J Obes 1989; 13:635-645.
108. Abell CA, Farquhar DL, Galloway SM et al. Placebo controlled double-blind trial of fluvoxamine maleate in the obese. J Psychosomatic Res 1986; 30:143-146.
109. De Zwaan M, Schönbeck G, Nutzinger D et al. Fluvoxamine and behavior therapy in the treatment of depressed obese. Pharmacopsychiatry 1989; 22:223.

110. Meryn S, De Zwaan M, Schoenbeck G et al. Effect of overweight and weight reduction with dietary therapy and/or fluvoxamine on liver function in obesity. Gasteroenterology 1990; 98:A607.
111. Szkudlarek J, Elsborg L. Treatment of severe obesity with a highly selective serotonin re-uptake inhibitor as a supplement to a low calorie diet. Int J Obes 1993; 17:681-683.
112. Goldstein DJ, Rampey AH, Enas GG et al. Fluoxetine: A randomized clinical trial in the treatment of obesity. Int J Obes 1994; 18:129-135.
113. Rutter JJ, Auerbach SB. Acute uptake inhibition increases extracellular serotonin in the rat forebrain. J Pharmacol Exp Ther 1993; 265:1319-1324.
114. Gundlah C, Martin KF, Heal DJ et al. In vivo criteria to differentiate monoamine reuptake inhibitors from releasing agents: sibutramine is a reuptake inhibitor. J Pharmacol Exp Ther 1997; 283:581-591.
115. Gottfries CG. Use of citalopram in syndromes related to 5-HT disturbance. Rev Contemp Pharmacother 1995; 6:307-313.
116. Blier P, de Montigny C. Current advances and trends in the treatment of depression. Trends Pharmacol Sci 1994; 15:220-226.
117. Artigas F, Perez V, Alvarez E. Pindolol induces a rapid improvement of depressed patients treated with serotonin reuptake inhibitors. Arch Gen Psychiatry 1994; 51:248-251.
118. Blier P, Bergeron R. Effectiveness of pindolol with selected antidepressant drugs in the treatment of major depression. J Clin Psychopharmacol 1995; 15:217-222.
119. Pérez V, Gilaberte I, Faries D et al. Randomised, double-blind placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment. Lancet 1997; 349:1594-1597.
120. Tome MB, Isaac MT, Harte R et al. Paroxetine and pindolol: A randomized trial of serotonergic autoreceptor blockade in the reduction of antidepressant latency. Int Clin Psychopharmacol 1997; 12:81-89.
121. Middlemiss DN, Blakeborough L, Leather SR Direct evidence for an interaction of β-adrenergic blockers with the 5-HT receptors. Nature 1977; 267:289-290.
122. Artigas F, Romero L, De Montigny C et al. Acceleration of the effects of selected antidepressant drugs in major depression by 5-HT_{1A} antagonists. Trends Neurosci 1996; 19:378-383.
123. Blier P, Seletti B, Bouchard C et al. Functional evidence for the differential responsiveness of pre- and postsynaptic 5-HT_{1A} receptors in the rat brain. Soc Neurosci Abs 1994; 20:1540.
124. Gartside SE, Umbers V, Hajós M et al. Interaction between a selective 5-HT_{1A} receptor antagonist and an SSRI in vivo: Effects on 5-HT cell firing and extracellular 5-HT. Br J Pharmacol 1995; 115:1064-1070.
125. Romero L, Bel N, Artigas F et al. Effect of pindolol on the function of pre- and postsynaptic 5-HT_{1A} receptors: In vivo microdialysis and electrophysiological studies in the rat brain. Neuropsychopharmacol 1996; 15:349-360.
126. Hjorth S. Serotonin 5-HT_{1A} autoreceptor blockade potentiates the ability of the 5-HT reuptake inhibitor citalopram to increase nerve terminal output of 5-HT in vivo: A microdialysis study. J Neurochem 1993; 60:776-779.
127. Arborelius L, Nomikos GG, Hertel P et al. The 5-HT_{1A} receptor antagonist (S)-UH-301 augments the increase in extracellular concentrations of 5-HT in the frontal cortex produced by both acute and chronic treatment with citalopram. Naunyn-Schmiedeberg's Arch Pharmacol 1996; 353:630-640.
128. Malagié I, Trillat A-C, Douvier E et al. Regional differences in the effect of the combined treatment of WAY 100635 and fluoxetine: An in vivo microdialysis study. Naunyn-Schmiedeberg's Arch Pharmacol 1996; 354:785-790.
129. Invernizzi R, Velasco C, Bramante M et al. Effect of 5-HT_{1A} receptor antagonists on citalopram-induced increase in extracellular serotonin in the frontal cortex, striatum and dorsal hippocampus. Neuropharmacology 1997; 36:467-473.
130. Kerrigan F. Antidepressant patents: 1995-1997. Exp Opin Ther Patents 1998; 8:439-460.
131. Pazos A. Palacios JM. Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors. Brain Res 1985; 346:205-230.

132. Sotelo C, Cholley B, El Mestikawy S et al. Direct immunohistochemical evidence of the existence of 5-HT_{1A} autoreceptors on serotonergic neurons in the midbrain raphe nuclei. Eur J Neurosci 1990; 2:1144-1154.
133. De Vry J. 5-HT_{1A} receptors in psychopathology and the mechanism of action of clinically effective therapeutic agents. Drug News and Perspectives 1996; 9:270-280.
134. Tricklebank MD, Forler C, Fozard JR. The involvement of subtypes of the 5-HT_1 receptor and catecholaminergic systems in the behavioural response to 8-hydroxy-2-(di-*n*-propylamino)tetralin in the rat. Eur J Pharmacol 1985; 106:271-282.
135. Oksenberg D, Peroutka SJ. Antagonism of 5-hydroxytryptamine$_{1A}$ (5-HT_{1A}) receptor-mediated modulation of adenylate cyclase activity by pindolol and propranolol isomers. Biochem Pharmacol 1998; 37:3429-3433.
136. Luscombe GP, Martin KF, Hutchins LJ et al. Mediation of the antidepressant-like effect of 8-OH-DPAT in mice by postsynaptic 5-HT_{1A} receptors. Br J Pharmacol 1993; 108:669-677.
137. Aulakh CS, Wozniak KM, Haas M et al. Food intake, neuroendocrine and temperature effects of 8-OHDPAT in the rat. Eur J Pharmacol 1988; 146:253-259
138. De Vivo M, Maayani S. Stimulation and inhibition of adenylyl cyclase by distinct 5-hydroxytryptamine receptors. Biochem Pharmacol 1990; 40:1551-1558.
139. Yocca FD, Wright RN, Margraf RR et al. 8-OH-DPAT and buspirone analogs inhibit the ketanserin-sensitive quipazine-induced head shake response in rats. Pharmacol Biochem Behav 1990; 35:251-254.
140. Zhang L, Barrett JE. Modification of the discriminative stimulus effects of 8-OH-DPAT, buspirone and the β-adrenoceptor antagonist pindolol after chronic administration of the 5-HT_{1A} agonist 8-OH-DPAT in the pigeon. Behav Pharmacol 1991; 2:369-378.
141. Moore NA, Rees G, Sanger G et al. 5-HT_{1A}-mediated lower lip retraction: effects of 5-HT_{1A} agonists and antagonists. Pharmacol Biochem Behav 1993; 46:141-143.
142. Przegalinski E, Tatarczynska E, Chojnacka-Wójcik E. The role of hippocampal 5-hydroxytryptamine$_{1A}$(5-HT_{1A}) receptors in the anticonflict activity of β-adrenoceptor antagonists. Neuropharmacology 1995; 34:1211-1217.
143. Bartoszyk GD, Hegenbart R, Ziegler H. EMD 68843, a serotonin reuptake inhibitor with selective presynaptic 5-HT_{1A} receptor agonistic properties. Eur J Pharmacol 1997; 322:147-153.
144. Rollema H, Clarke T, Sprouse JS et al. Combined administration of a 5-hydroxytryptamine $(5\text{-HT})_{1D}$ antagonist and a 5-HT reuptake inhibitor synergistically increases 5-HT release in guinea-pig hypothalamus in vivo. J Neurochem 1996; 67:2204-2207.
145. Davidson C, Stamford JA. 5-$HT_{1B/D}$ antagonists potentiate paroxetine's effect on 5-HT efflux in the lateral geniculate nucleus: In vivo voltammetric data. Biochem Soc Trans 1997; 25:49S.
146. Gobert A, Rivet J-M, Cistarelli L et al. Potentiation of the fluoxetine-induced increase in dialysate levels of serotonin (5-HT) in the frontal cortex of freely moving rats by combined blockade of 5-HT_{1A} and 5-HT_{1B} receptors with WAY 100,635 and GR 127,935. J Neurochem 1997; 68:1159-1163.
147. Roberts C, Price GW, Jones BJ. The role of 5-$HT_{1B/1D}$ receptors in the modulation of 5-hydroxytryptamine levels in the frontal cortex of the conscious guinea pig. Eur J Pharmacol 1997; 326:23-30.
148. Broderick PA, Piercey MF. 5-HT_{1A} agonists uncouple noradrenergic somatodendritic impulse flow and terminal release. Brain Res Bull 1991; 27:693-696.
149. Haddjeri N, de Montigny C, Blier P. Modulation of the firing activity of noradrenergic neurones in the rat locus coeruleus by the 5-hydroxytryptamine system. Br J Pharmacol 1997; 120:865-875.
150. Baumann PA, Waldmeier PC. The effects of blockade of presynaptic α-receptors by yohimbine and mianserin on the levels of 4-hydroxy-3-methoxyphenethyleneglycol sulphate (MOPEG-SO_4) in different brain regions of the rat. Influence of mianserin on daily rhythm in MOPEG-SO_4 level. Experientia 1978; 34:922.
151. L'Heureux R, Dennis T, Curet O et al. Measurement of endogenous noradrenaline release in the rat cerebral cortex in vivo by transcortical dialysis: Effects of drugs affecting noradrenergic transmission. J Neurochem 1986; 46:1794-1801.

152. Dennis T, L'Heureux R, Carter C et al. Presynaptic alpha-2 adrenoceptors play a major role in the effects of idazoxan on cortical noradrenaline release (as measured by in vivo dialysis in the rat). J Pharmacol Exp Ther 1987; 241:642-649.
153. Reynolds LS, Braselton JP, Sprouse JS et al. In vivo profile of CP-93,393: Evidence of combined 5-HT_{1A} agonist and α2 antagonist activities. Soc Neurosci Abs 1995; 21:827.5.
154. Schmidt AW, Fox CB, Lazzaro J et al. CP-93,393, a novel anxiolytic/antidepressant agent with both 5-HT_{1A} agonist and alpha-2 adrenergic antagonist properties: In vitro studies. Soc Neurosci Abs 1995; 21:827.4.
155. Stassen HH, Delini-Stula A, Angst J. Time-course of improvement under antidepressant treatment: A survival-analytical approach. Eur Neuropsychopharmacol 1993; 3:127-135.
156. Norman TR, Leonard BE. Fast-acting antidepressants—can the need be met? CNS Drugs 1994; 2:120-131.
157. Laska EM, Siegel C. Characterisation onset in psychopharmacological clinical trials. Psychopharmacol Bull 1995; 31:29-35.
158. Montgomery SA. Are 2-week trials sufficient to indicate efficacy? Psychopharmacol Bull 1995; 31:41-44.
159. Overall JE. Justifying a "fast acting" claim for antidepressant drugs. Psychopharmacol Bull 1995; 31:45-55.
160. Richelson E, Pfenning M. Blockade by antidepressants and related compounds of biogenic amine uptake into rat brain synaptosomes: most antidepressants selectively block norepinephrine uptake. Eur J Pharmacol 1984; 104:277-286.
161. Bolden-Watson C, Richelson E. Blockade by newly-developed antidepressants of biogenic amines into rat brain synaptosomes. Life Sci 1993; 52:1023-1029.

Patents

American Home Products Corp., GB2303303 (1997).
Eli Lilly & Co., EP-687472 (1995).
Eli Lilly & Co., EP-714663 (1996).
Eli Lilly & Co., EP-759299 (1997).
Pierre Fabré Medicament, WO9728141 (1997).
Pfizer, Inc., WO9603400 (1996).
Pfizer, Inc., EP-701819 (1996).
SmithKline-Beecham PLC, WO9531988 (1995).

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